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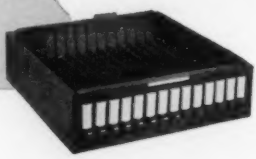

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The New Brookhaven Biology Building and "Gamma Field"

THE completion of the new biology building at Brookhaven National Laboratory allows the extensive use of the research facilities of that laboratory. The organization of the laboratory, which is operated by Associated Universities, Inc. for the Atomic Energy Commission, represents an experiment in the method of conducting basic research in biology. Now well started, it is an attempt to bring university biologists into close association with the newer advances in the physical sciences in order to utilize these ideas and techniques in the solution of basic biological problems. Many of the instruments and techniques involved in work of this kind are very specialized and require extensive facilities or experience to be utilized effectively.

The building itself is a modern laboratory designed to house virtually all phases of biology, and includes extensive animal quarters. All laboratories are equipped to work with radioactive materials, and in addition there is a "hot laboratory" where large quantities of radioactive material can be handled safely. There are two large greenhouses as well as a "radiation" greenhouse in which is located a 7 curie Co^{60} gamma ray source, so plants can be grown under the influence of gamma rays.

In addition, there are a number of special facilities, chief among them being the "gamma field." This is a 10-acre field which currently has a 2200 curie Co^{60} source at its center. Plants are grown at various distances from the source to give various radiation intensities. There is a thermal neutron facility at the reactor where plants and animals can be treated with thermal neutrons, virtually uncontaminated with other radiations, and also a fast neutron facility for similar treatments with fast neutrons uncontaminated with other radiations. There are several high energy accelerators available for biological experiments.

Only a small proportion of the research staff is in residence on a permanent basis, while the rest is at the laboratory for limited periods of time in order to develop an idea requiring special facilities, or to develop special techniques which can later be incorporated in research at a university. Some of these are on leave from universities, some on fellowships, some have no definite university connection but are looking toward a university career, and some are graduate students engaged in their thesis research. The policies with regard to the staff are designed to provide a continuously rotating staff, but with enough permanent members to give the program stability.

The department has been in existence about five years, and the general features of the research program are crystallizing. The chief tool so far used is ionizing radiation, in various forms and in connection with a number of different problems. The first type of study is one of the effects of radiations on biological material, which throws light on normal life processes, especially in plants, whose growth and differentiation can be profoundly altered by radiation. Plants growing in the gamma field may be either badly stunted or stimulated depending on the dosage rate, species, and the characteristic under investigation. Ionizing radiation has proved to be a useful tool in the study of genetic problems including the nature of the mutation process. Addition of fast and slow neutrons to the available radiations is very important, since it is increasingly apparent that neutrons produce biological effects by quite a different mechanism than do electromagnetic radiations.

A cooperative project is being inaugurated between Brookhaven and a number of agricultural experiment stations in which the attempt is being made, on a scale large enough to obtain definitive answers, to produce agriculturally-important mutations by radiation. The material is being irradiated in various ways at Brookhaven and then sent to the experiment stations for screening.

Another extensive activity relating to both plants and animals is the use of radioactive isotopes. Laboratories equipped to work with these in tracer quantities are becoming quite common, so at the present time the unique facilities of the Brookhaven laboratory consist largely of equipment to work with large amounts of material or with isotopes having very short half-lives.

With the completion of the new building the department is now able to house a staff of about a hundred persons, including scientists, students, and technicians. In line with the growing importance of quantitative methods and the newer techniques, the staff includes persons representing many aspects of biology.

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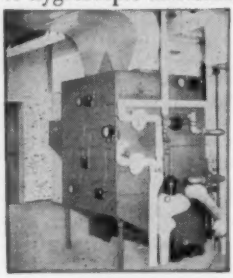

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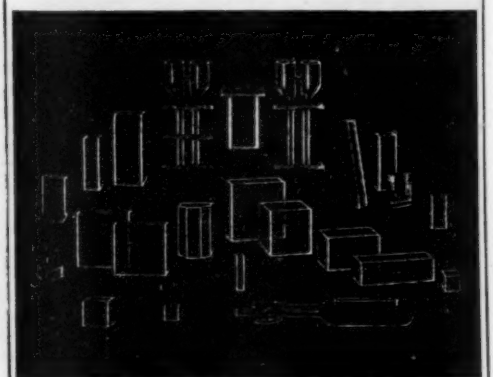

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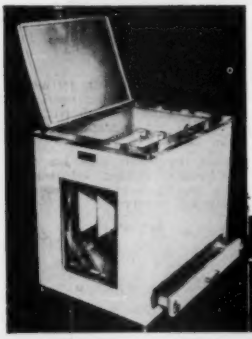

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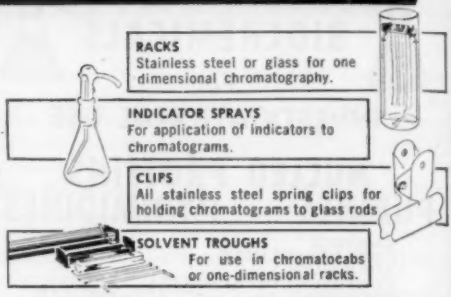

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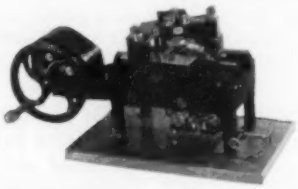

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Sex in Bacteria: Genetic Studies, 1945–1952[1]

Joshua Lederberg[2] and E. L. Tatum

Department of Genetics, University of Wisconsin, Madison, and
Department of Biological Sciences, Stanford University, Stanford, California

FOR MANY YEARS bacteria were considered biologically exceptional organisms with no genes, nuclei, or sex, although the recognition of their biochemical similarities to other forms of life constituted one of the main foundations of comparative biochemistry. Over the last decade evidence has accumulated which has led to the satisfying conclusion that bacteria are not biologically unique but possess genetic and behavior systems more or less analogous to those of other forms, including nuclei, genes, and in certain instances even true sexual mechanisms for recombination of unit characters.

Historically, this change in our thinking in regard to bacteria stems from the pioneer concepts of Lwoff (1938) and Knight (1936) relating the nutritional requirements of mieroorganisms to an evolutionary loss of synthetic abilities. If such losses in microorganisms were based on mutation and selection as required by modern concepts of evolution, the capacities for synthesis of essential nutrilites in microorganisms should be determined by genes, which should be subject to mutation, as are most genes in other organisms. Such considerations led Beadle and Tatum (1941) to the successful production by irradiation of nutritionally deficient or biochemical mutants in the heterothallic ascomycete *Neurospora,* and to the establishment of the genic basis of biochemical reactions leading to the synthesis of amino acids and vitamins. This relation has since been amply substantiated and extended by further work with *Neurospora* and other sexual microorganisms (cf. Tatum and Perkins, 1950).

The next step in the evolution of our concepts of bacterial genetics was the experimental application of the *Neurospora* techniques to the production of biochemical mutants in these simpler organisms. The first nutritionally deficient (auxotrophic) mutants were produced in 1944 by x-ray treatment of *Escherichia coli* and *Acetobacter melanogenum* (Gray and Tatum, 1944; Roepke *et al.,* 1944). Subsequently, auxotrophic mutants have been obtained in almost every species of bacteria investigated (see Tatum, 1946; Tatum and Perkins, 1950). In addition to mutations to growth-factor dependence and reverse mutation to growth-factor independence, other types of mutant characters have been obtained, thoroughly investigated, and proved extremely valuable. These include such characters as virus resistance, antibiotic resistance, and capacity for sugar utilization.

The first auxotrophic mutants were obtained by the tedious and laborious process of plating out irradiated cells on fully supplemented medium, and then isolating individual colonies which were subsequently examined for failure to grow in the simple synthetic medium adequate for the original stock (minimal medium). The specific requirements of these deficient clones were then determined by systematic supplementation of the minimal medium with known growth-factors.

Later improvements in techniques have eliminated much of the labor involved in isolating and testing mutants of bacteria, particularly *E. coli.* These include (cf. Lederberg 1950, 1951a) the layer-plate technique in which only presumptive mutants are isolated for further testing, and the penicillin method in which non-mutants are actively eliminated, leaving mutant cells which form colonies after removal of the antibiotic and suitable supplementation of the medium. A further modification of this method, using solid medium and penicillinase, permits easy isolation of any desired type of auxotroph (Adelberg and Myers, 1952), and the isolation and testing of strains has been still further simplified by the replica plating method (Lederberg and Lederberg, 1952) which in a single operation permits transferring all colonies on a plate to a number of other plates with different supplements.

By all available criteria it is now generally accepted that most, if not all, characteristics of bacteria are controlled by hereditary units, and that these hereditary units in bacteria are analogous with genes in classically sexual organisms in the independence and randomness of their mutation, the effect of physical and chemical agents on their mutation frequency, and qualitatively in the types of biochemical and enzymatic effects of their mutation (cf. Tatum and Perkins, 1950).

After establishment of this functional analogy between genes of bacteria and those of sexual forms, the next step logically was to ask if the analogy could be carried further, and if a mode of inheritance of bacterial characters similar to the Mendelian process in higher types could be detected. Although a number of workers had looked for character recombination in bacteria, and other microorganisms, even as early as 1908 (Browning, 1908; for other important references cf. Tatum and Lederberg, 1947), in most cases the biological materials available were not adequate for a definitive experimental test, although some sug-

[1] This paper was prepared in connection with a Symposium on Sex in Microorganisms, held in December 1951 and to be published in a forthcoming volume by the AAAS.

[2] Paper No. 498 of the Department of Genetics. This work has been supported by research grants (E72) from the National Microbiological Institute, National Institutes of Health, Public Health Service, and from the Research Committee, Graduate School, University of Wisconsin, with funds provided by the Wisconsin Alumni Research Foundation.

gestive evidence of a circumstantial nature has been obtained. The definitive nature of auxotrophic mutants and the relative ease of their isolation and diagnosis provided ideal material for testing the possibility of recombination of hereditary units in bacteria.

The independent occurrence and expression of auxotrophic mutations in *E. coli* permitted building up multiple mutant stocks of *E. coli* strain K-12 with several deficiencies by successive mutational treatment (Tatum, 1945). In this way, for example, cultures Y-10, requiring threonine, leucine, and thiamin, and 58-161, requiring biotin and methionine, were obtained. For simplicity in considering its capacity for synthesis of the factors concerned, strain 58-161 can be represented as biotin– methionine– threonine+ leucine+ thiamin+ (*B– M– T+ L+ B_1+*), while strain Y-10 would similarly be represented as *B+ M+ T– L– B_1–*. In this representation, in analogy with other organisms such as *Neurospora*, the genes determining alternative characters (*B+* and *B–* for example) are considered allelic.

Accordingly, a sexual process in a mixed culture of these two strains would involve reshuffling the indicated alleles at these five loci. If this were at random, any recombination might be expected, and might have been looked for. However, recombination to give a nutritionally independent type (prototroph) would be most easily detected, since it alone would grow on minimal medium, whereas any dependent types, including both parental strains, would not.

Experimental tests were carried out (Tatum and Lederberg, 1947) by growing the two strains either separately or together in complete media, then centrifuging out the cells, washing repeatedly to remove growth-factors, and plating mixtures of the washed cells into minimal agar. The results were striking in that about 100 colonies developed for each 10^9 cells examined, and on reisolation and purification these maintained their prototrophic character. Similarly treated single cultures of each strain gave no colonies on the minimal medium. This would be expected on the basis of the low frequency of mutation of each character to independence (*ca.* 1 in 10^7 cells) since the derivation of a prototroph from a triply deficient strain would then occur with a frequency of 1 in 10^{21} cells.

The simplest explanation for these results therefore appeared to be that gene recombination took place to give the prototroph *B+ M+ T+ L+ B_1+*, as shown in Fig. 1. Other possibilities, such as association of cells, or the formation of unsegregated diploid, or of heterocaryotic cells were made unlikely by various experimental tests which established the homogeneity and uniqueness of the derived prototrophs (cf. Tatum and Lederberg, 1947).

The only alternative to a sexual recombination seemed therefore a type of unilateral change by a noncellular transforming principle similar to that involved in induced changes of type in the pneumococcus (Austrian, 1952). Two lines of evidence made this improbable. First, cell-free filtrates gave no prototrophs and direct contact of the cells themselves seemed essential, as shown by growing the two types separated by an ultra-fine sintered glass bacterial filter (Davis, 1950). Second, the successful recovery of most of the possible recombination types in later

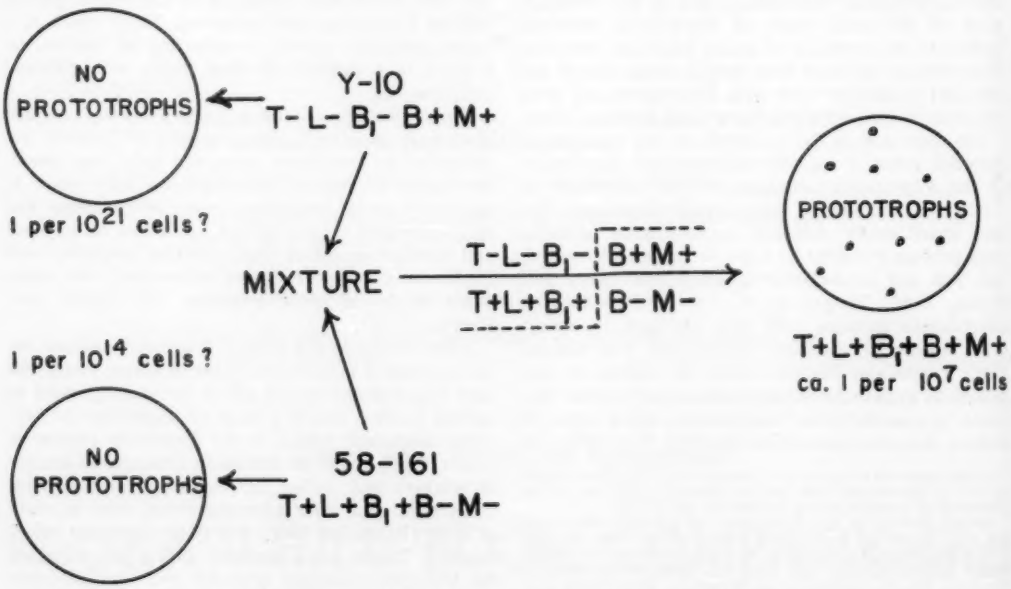

FIG. 1. Diagrammatic representation of recombination in prototrophs.

crosses involving a much greater variety of characters, including resistance to antibiotics and viruses and sugar fermentation characters, would necessitate simultaneous transformation in different directions for different characters, and in both directions in different cells.

Thus the results of experiments of the type described above are satisfactorily explained only as resulting from a sexual mating process, followed by reassortment or segregation of genetic material. Repetition and extension of these experiments in a considerable number of laboratories during the past five years have amply confirmed the reality of the essential phenomenon and the validity of this conclusion.

These experiments have added considerable information about environmental factors affecting the recombination process, and support the concept that direct cell contact is necessary for the sexual process. Some of the strongest support comes from the demonstration by Nelson (1951) that recombination behaves as a bimolecular reaction, as if factors such as relative and absolute concentrations of the two types of cells which would affect the frequency of contact of appropriate cells, similarly affect frequency of recombination. The experiments of Davis (1950), showing the need for cell contact, and in a more positive sense the production of a genetically diploid cell (Lederberg, 1949) likewise support the postulated occurrence of a cell to cell sexual process in *E. coli* K-12.

The intimate details of mating are still obscure. Owing to its infrequency we have been discouraged (until very recently) from any serious attempts to detect its morphological basis, and were obliged to be content with genetic inferences. E. Klieneberger-Nobel, of the Lister Institute, London, England, has made a most painstaking study of mating cultures of *E. coli* K-12 (unpublished work, quoted by her kind permission). Although she occasionally observed what appeared to be stages in the abortive development of L-forms (Klieneberger-Nobel, 1951), she was unable to correlate them in any way with recombination. The only conclusion that is warranted is that recombination in *E. coli* does not involve spectacular formations, such as have been observed and speculated about in many bacteria. The possibility of a mating process involving a rapid conjugation and separation of the parent cells, without the intervention of special gamete or zygote structures, has not been excluded and is perhaps most likely.

The recently reported work of Hayes may throw further light on the conjugation process. Working with a single pair of K-12 stocks, Hayes (1952a) found that streptomycin treatment sterilized one (58-161) without affecting its recombination potency, but completely abolished recombination potency of the other (W677), and he postulated a unidirectional transfer of metabolically inert genic material from 58-161 to W677. The results of later studies (Hayes, 1952b) using ultra-violet irradiation for cell inactivation and stimulation of recombination (Clark *et al.*, 1950) were consistent with this hypothesis. He has suggested that the recombination may involve only a limited transfer of genic material, through a process which may not require the participation of two intact cells.

Granted the ability of *E. coli* K-12 to undergo a sexual recombination of genetic characters analogous to that found in other organisms, even if the morphological basis is still obscure, can the analogy be carried further? What evidence exists bearing on a chromosomal organization of the genes in *E. coli*? In all organisms that have been adequately studied, the genes are arranged in a linear order on chromosomes, whose distribution at cell division and during the formation of gametes follows very precise laws. It is difficult, in fact, to conceive of any other arrangement of the genes that would permit their regular and orderly distribution to the products of each cell division, without an uneconomical redundancy of the genetic factors for different traits. But aside from these speculations, there is considerable experimental evidence that the genes of *E. coli* are organized in linear order on one or more chromosomes (Lederberg, 1947; Rothfels, 1952; Lederberg *et al.*, 1951).

In the crosses mentioned so far, all the differences between the parents are directly involved in the selection of recombinants, so that we had no opportunity to investigate the segregation of factors whose expression is not enforced by the selective method. A number of mutant characters have been discovered, however, which are indifferent to plating on minimal medium. They include differences in the fermentation of various sugars, resistance to antibiotics, and resistance to phages. Such characters will be called unselected, since their segregation is regulated by the internal mechanism of recombination rather than the exigencies of the technique.

The first unselected marker to be used in our experiments was resistance to phage T1 (Tatum and Lederberg, 1947). According to conventions, resistance and sensitivity are symbolized as V_1^r and V_1^s, respectively. V_1^r is a specially convenient marker, as it can be produced in any stock by the selection of spontaneous mutants with T1. Before they can be used in these experiments, such stocks must be carefully purified and, as for any marker, the stability and reproducible scoring of the mutation must be verified. A variety of crosses was carried out in which one parent was V_1^r, the other V_1^s. In each case we found a segregation for this marker, i.e., some of the prototrophs displayed the V_1^r trait, from one parent, and others V_1^s from the other. In control crosses, $V_1^s \times V_1^s$ gave only V_1^s, and $V_1^r \times V_1^r$ gave only V_1^r. Such a segregation in the first filial generation, the f-1, indicates a haplobiontic life cycle, similar to that of many unicellular organisms.

If an unselected marker were associated with one chromosome independent of others carrying the selected, nutritional mutations, the f-1 should show a mendelian ratio of 1:1. Different ratios were ob-

served for each of the markers tested, the first evidence of linkage. The observed frequencies varied from one marker to another, and with a given marker, from one parental combination to another. In a given cross, however, the f-1 segregation ratios have been as reproducible as in any genetic material, which is to say they are subject mainly to sampling error.

A simple test of the significance of f-1 ratios can be made by reverse crosses, whereby a marker is introduced first in one, then in the other parent. For example, *BM– V1 × TL– V1* is compared with *BM– V1 × TL– V1*. About 70% of the prototrophs from the first cross are *V1*. In the second cross, about 30% are *V1*, i.e., this ratio is inverted. The same result has been obtained in many reverse crosses involving different parental lines, and different markers and combinations of markers. It shows that the f-1 ratios have nothing to do with the physiological effects of the markers, but that they are due entirely to the mechanics of segregation. It also shows that dominance plays no role, and more generally that a genetic particle controlling each observed trait has been segregated, and is represented only once in the genotype of the recombinant cell.

By compounding elementary principles, genetic maps of *E. coli* can be constructed from segregation data involving numerous unselected markers (Cavalli, 1950; Newcombe and Nyholm, 1950; Rothfels, 1952; Lederberg *et al.*, 1951). By using other methods, the auxotroph mutations can be relieved of their burden of the selection of recombinants, and thus handled as unselected markers also. About half of the known markers of *E. coli* K-12 have been satisfactorily located in a single linear linkage group. Other markers have displayed a more confusing behavior which does not fit any scheme very satisfactorily, but is probably a result of rather complex chromosomal aberrations, for which there is independent evidence from the study of exceptional diploids (*v. infra*). It was long thought that *E. coli* had only one chromosome, but more recent evidence points to at least two, the segregation of which is not, however, entirely independent for secondary reasons (Fried and Lederberg, 1952). Cytological observations on haploid K-12 cultures have been interpreted by DeLamater (1952) as signifying three chromosomes, but further work is needed for the detailed concordance of genetic with cytological findings. Cytological study of *E. coli* has so far been confined to vegetative cells, whereas the genetic studies deal principally with segregation at meiosis.

The difficulties, briefly mentioned, in the segregation of certain misbehaving markers might appear to be fatal to a straightforward sexual interpretation of recombination except for the confirmatory evidence provided by exceptional diploid cultures. In ordinary crossings, the diploid condition has been inferred from its consequences of recombination and segregation, but is not directly observed. In 1946–47, many unsuccessful attempts were made to secure artificial diploids with agents such as camphor, acenaphthene, colchicine, and heat shocks, which have been used for other organisms (cf. Roper, 1952). More recently, however, a mutation, *Het*, occurred in one of our stocks which serves the same purpose (Lederberg *et al.*, 1951). Little is known of the action or genetic transmission of *Het*, but when it is present in one or both parents of a cross, several per cent of the prototrophs prove to be persistent heterozygotes. These heterozygous cultures continually segregate the alternative markers brought in by the parents. Thus diploid cells heterozygous for lactose fermentation, *Lac+/Lac–*, produce mosaic colonies on an indicator medium, as shown in Fig. 2. The dark or "+" sectors consist of still heterozygous cells, *Lac+/Lac–*, and of *Lac+* haploid segregants; the light or "–" sectors are *Lac–* haploid segregants. On complete medium, the faster-growing haploid cells soon outstrip the original diploids, but segregation can be effectively prevented on a minimal medium owing to the nutritional requirements of the haploid components. Single cell studies (Zelle and Lederberg, 1951) have verified that genetic factors from two parents have converged to a single hybrid cell, the essence of sexuality.

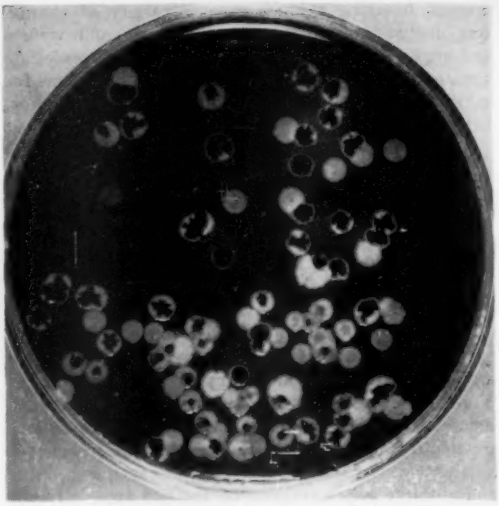

FIG. 2. Segregating diploid culture plated on indicator agar, showing variegated colonies.

Haploid and diploid cultures have been studied cytologically, especially for comparisons of their nuclear structure, by means of the Piekarski-Robinow technique (osmic fixation; HCl hydrolysis; Giemsa stain; mount in Abopon). This method gives brilliant nuclear preparations, but *E. coli* appears to be technically unsuitable for unequivocal demonstration of mitotic figures, as claimed in the pioneering and provocative work of DeLamater and his associates (1951). Although nuclear aggregates that are very suggestive of mitotic metaphases and anaphases can be found with a brief search, definitive interpretations of *E. coli* cytology depend for the most part on the

validity of the conclusions that have been drawn from technically superior material. It is difficult for a geneticist to imagine how bacteria could get along without some sort of mitotic process, but its details require critical, and objective definition. The comparisons of haploid and diploid *E. coli* have revealed consistent and unequivocal differences, as shown in photographs published elsewhere (Lederberg *et al.*, 1951). The determination whether the diploids show a doubling of the chromosome number is not yet subject to independent, objective verification.

The correlation of genetic heterozygosity with nuclear complexity is only a small step in the direction of a bacterial cytogenetics. It has been furthered by Witkin's studies, in which the segregation of mutant genes during fission has been correlated with the nuclear plurality of the bacterial cells at the time the mutations were induced (Witkin, 1951). These observations do accord, however, with a chromosomal theory of inheritance and sexuality in *E. coli*.

The work cited so far has been done with derivatives of a single strain, K-12, of *Escherichia coli*. A few early attempts to duplicate genetic recombination in other *E. coli* strains popular in genetic work were quite unsuccessful. Cavalli and Heslot (1949) discovered a culture in the British Type Culture Collection, NTCC 123, that was fertile with K-12, but a special screening method had to be developed before many new strains could be effectively studied (Lederberg, 1951a). Of nearly 2,000 independent isolations of *E. coli* from various sources, over fifty have proven to be cross-fertile with K-12, and so far as has been tested, with each other. All of the new strains conform to the type *E. coli*, except for an occasional minor deviation, but are otherwise as heterogeneous as any sample of strains. They are serologically quite diverse: an immunogenetic study has been initiated which has so far put the antigens of *E. coli* on the same basis as the mammalian blood groups.

One important reason for undertaking this study of new strains was to investigate the sexual compatibility relations of *E. coli*. Until recently, several lines of evidence conspired to substantiate the idea that *E. coli* K-12 was homothallic. The crossable strains are all derived from a single pure culture. Several workers had suggested that a mating-type system might be obscured by mutations from one mating type to the other, as occurs in certain yeasts. However, this hypothesis was rejected because no segregation of mating preferences was observed from heterozygous diploids, as would have been expected from a heterothallic mating. It has since been discovered that a unique compatibility mechanism does operate in *Escherichia coli* (Lederberg, Cavalli, and Lederberg, 1952). The involved history of this discovery must be detailed elsewhere, and only the general conclusions can be given here.

Wild type K-12 carries a hereditary factor, *F+*, which is required for mating. Similarly, most of the auxotrophic mutants of K-12 are *F+*, and therefore mutually compatible, but the much used line descended from the threonine-leucine mutant, 679-680 (Tatum, 1945), is *F−*. Because most of the other tester cultures are *F+*, however, the *F−* "mutation" was not detected in earlier experiments. The empirical definition of *F−* is that crosses of two *F−* parents are completely sterile, although comparable crosses in which one or both parents is *F+* are productive. The self-incompatibility of *F−* has been detected in two ways: sublines of 679–680 are mutually incompatible, and new occurrences of the *F−* "mutation" have been discovered which are incompatible with 679–680. The *F−* "mutation" is given in inverted commas because its inheritance and transmission set it apart from all of the other markers so far studied.

All the progeny of crosses within strain K-12 are *F+*, whether the parents were *F−* × *F+* or *F+* × *F+* [*F−* × *F−* cannot, of course, be tested]. This was explained by the finding that F+ was contagious, that is that growing *F−* cells in mixture with *F+* resulted in many of the former (identified by other genetic markers) becoming permanently *F+*. As many as 50 per cent of the originally *F−* cells may become *F+* by this conditioning process within a few hours. "*F+*" is therefore tentatively regarded as an infective, virus-like agent, but this has not yet been confirmed by the isolation of "*F+*" in a cell-free preparation. The transmission of *F+* is not accompanied by the transfer of any other marker, so far as is known.

The virus-like properties of the compatibility factor have led to some speculation on its relationship to a virus known to be present in *E. coli* K-12, the latent bacteriophage λ. This question has been studied in some detail, and it can be asserted that λ is not related in any way to genetic recombination or to the sexual compatibility mechanism. Non-lysogenic, i.e., λ-free cultures are fully compatible in sexual recombination, and the transfer of *F+* is independent of the transfer of λ, which unlike *F+*, can readily be obtained in cell-free filtrates. Genetic studies of lysogenicity (Lederberg and Lederberg, 1953) have, however, demonstrated a close relationship between this latent virus and the chromosomes of the bacterial host.

The details of the compatibility system are being studied at the present time. It has been noted that *F+* × *F+* crosses tend to be considerably less productive than comparable *F+* × *F−*. Many of the results are consistent with the concept of relative sexuality as noted in many algae and fungi. That is to say, different cultures can be arranged in sequence of relative potencies, such that the productivity of a cross will be related to the difference in potency of the two parents. In *E. coli* K-12, the relative potency can be controlled both by environmental variations, and by genotypic effects. Within K-12, differences in the *F+* agent itself have not been found. However, the *F+* state as conditioned by some other wild-type strains appears to be unstable in K-12 cells, suggesting the possibility of genetic differences in the presumed agent itself.

The genetic basis of the observed "mutations" to *F*– in strain K-12 is not known, and these have not been experimentally reproducible. Many wild type strains are *F*– (i.e., non-infective) but retain their compatibility status, so that it is impossible to generalize on the causes of sterility or compatibility in the species *E. coli* taken as a whole.

In the absence of direct morphological evidence of sexual fusions, the principal alternative explanation for genetic recombination in *E. coli* has been "transformation" or "transduction." The biology of bacterial transformations is not very well understood (Ephrussi-Taylor, 1951; Austrian, 1952); in many ways it may be constructive to regard them as a limited form of hybridization. The chief distinction between transduction and sexual recombination is that the former seems to involve only a very small part of the whole genotype of the bacterium at each transfer (as in the capsular transformations in the pneumococcus), whereas sexual reproduction allows reassortment of the entire genotype of each parent, as in *E. coli*. The former seems to be correlated with an active unit that is morphologically and chemically much simpler than the intact cell; in *E. coli*, no unit other than the cell has been shown to be active in recombination.

A search for recombination in *Salmonella typhimurium*, a species distantly related to *E. coli*, has led to the discovery of another mode of transduction. In this system occasional bacteriophage particles appear to become fortuitously contaminated with genetic fragments from the host cells on which they are grown, and to be able to transduce these fragments to new cells which they may invade without killing them. The fragments retain their activity, and somehow enter the genetic organization of the new host. In this way, for example, flagellar antigenic traits from *S. typhimurium* may be introduced into cells of *S. typhi* to give a hybrid serotype or species not previously described (Zinder and Lederberg, 1952). The possibilities that sexual recombination may occur in *Salmonella*, or that a genetic transduction may be found in *E. coli* are not unlikely, in view of the taxonomic relationship of these bacteria. It is from a superposition of these phenomena in a single species that we may expect to learn the most about each of them. At present, however, they appear to be quite distinct.

To sum up the present status of our knowledge of sexuality in *E. coli*, it has been shown that in mixed cultures under suitable conditions a small but significant number of cells of certain strains of this organism undergo a process of recombination of genes governing a wide variety of characters. This process apparently involves a cell-to-cell contact, and presumptively copulation, or conjugation, with zygote formation. Analysis of the recombination products indicates that the genes are present in linear order on one or more chromosomes. In essence, then, certain strains of *E. coli*, especially K-12, are capable of a sexual process, analogous in so far as it has yet been analyzed to that of other organisms.

It is to be hoped and expected that sexual phenomena will not be limited to *E. coli* among the bacteria. It is likewise to be hoped that the significance of suggestive cytological phenomena in bacteria such as apparent conjugation tubes (DeLamater, 1951), star-body formation (Braun and Elrod, 1948), filterable L-forms (Klieneberger-Nobel, 1951) and large bodies (Dienes, 1946; Stempen and Hutchinson, 1951), can be further evaluated by genetic analysis involving the recombination and tracing of suitable genetic markers.

The future also holds not only promise of correlation of genetic and morphological aspects of conjugation and meiosis in *E. coli*, but the even more exciting prospects of discovering, elucidating, and correlating different modifications of sexuality and transfer of genetic material in microorganisms. With a clearer understanding of these relationships, the bacteria may be expected to occupy an increasingly important place in the study of the comparative biology of sex.

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News and Notes

Meeting of the APS Division of Fluid Dynamics

THE divisional meeting of the American Physical Society Division of Fluid Dynamics met at The Pennsylvania State College, July 1–3, 1953. More than one hundred participants took part in the meeting and contributed to a lively discussion. Two symposia, one on hydrodynamics (J. H. McMillen, chairman) and another on rarefied gases (F. J. Weyl, chairman) were organized, each with three invited papers. Twenty-five contributed papers presented during three sessions (W. Bleakney, F. N. Frenkiel, and R. G. Stoner, chairmen) covered several problems in fluid dynamics including papers on transonic, supersonic and hypersonic flows, shock waves in solids and fluids, boundary layer and turbulence research, and several other topics.

After a banquet of the Division, an after-dinner speech on education and research in fluid dynamics was given by R. J. Seeger of the National Science Foundation.

During the symposium on hydrodynamics W. E. Cummins discussed the work done at the David Taylor Model Basin on forces and moments acting on a body in a time varying potential stream. The recent investigations made at the Iowa Institute of Hydraulic Research were described by J. S. McNown and the problem of the compressibility and thermal effects in cavitation was treated by F. R. Gilmore of the California Institute of Technology.

At the symposium on rarefied gases H. Grad of the New York University considered the validity of the Boltzmann equation, and experimental data on frictional phenomena in rarefied air, measured at the University of California at Berkeley, were reported by S. A. Schaaf. The hydrodynamical theory of absorption and dispersion of ultrasonic waves was the subject of a paper presented by C. Truesdell of Indiana University.

A. R. Kuhlthau reported on viscous drag measurements on a rarefied gas using the high rotational speed techniques developed at the University of Virginia. Hypersonic flow was discussed in three papers: S. I. Pai presented some theoretical results for an insulated flat plate at large angles of attack, F. K. Hill reported recent work on boundary layer flow at the Johns Hopkins Applied Physics Laboratory, and A. Hertzberg and W. E. Smith described the hypersonic facilities of the Cornell Aeronautical Laboratory. G. E. Solomon reported experimental measurements at transonic speeds made at California Institute of Technology, and some theoretical results for unsteady transonic flow were discussed by E. Mollo-Christensen. Work done at the Los Alamos Scientific Laboratory on shock waves in solids was the subject of two papers; one on an experimental method to determine the equation of state from shock wave measurements by R. H. Christian and J. M. Walsh, another on the separation of a shock wave into elastic and plastic waves by S. Minshall. Shock compression in ducts and diffusers was discussed by J. Lukasiewicz of the

National Aeronautical Establishment of Canada and further observations of shock refraction made in The Pennsylvania State College shock tube were presented by R. G. Stoner, E. B. Davies, and D. C. Peckham. A curious phenomenon of degeneration of a shock wave into sound was observed by E. F. Cox at the Nevada Proving Ground and the theory of the transmission of a sound pulse through a shock wave was re-examined by R. A. Alpher and R. J. Rubin. A somewhat related problem of pressure multiplication in reentrant corners was discussed by R. J. Heyman, A. Sherman, and T. Schiffman. From the Naval Ordnance Laboratory came two papers on supersonic flow: The first, by R. Lehnert and S. Hastings, concerned spin effects on base-pressure measurements; in a second paper the former author reported on the Reynolds number effects on spheres. Drag measurements, made in the Ballistic Research Laboratories pressurized range, were reported by V. E. Bergdolt and F. D. Bennett. An inexpensive Mach-Zehnder interferometer used in several shock waves studies at Princeton University was described by D. Weimer, W. Bleakney, and D. R. White. Some turbulence studies, made in France, were reported by J. Bass who has continued his work on space and time spectra during his visit at the University of California in Berkeley. The stability of isotropic turbulence was discussed by R. Betchov, and F. Gifford, Jr., reported on turbulent diffusion from a volume source with nonuniform initial distribution. The Pennsylvania State College Ordnance Research Laboratory contributed two papers on turbulent boundary layers: D. Ross treated the two-dimensional case and E. M. Uram the axisymmetric boundary layers in an adverse pressure gradient. Some problems concerning eddy thermodynamics were described by A. K. Blackadar and the unsteady flow of gas through porous media by J. S. Aronofsky. The production and measurement of surface ripples investigated at the University of Vermont was discussed by M. L. Walbridge, H. M. Smith, Jr., and L. A. Wood.

Several informal discussions on various other subjects interesting fluid dynamicists took place between the sessions.

Scientists in the News

Alan M. Chesney, Dean of the Medical Faculty of The Johns Hopkins University, since 1929 has retired as active head of the School of Medicine. Although giving up his administrative and academic duties, Dr. Chesney will continue his association with the Hopkins medical institutions in an emeritus capacity.

Dr. Chesney, a native of Baltimore, first came to the Hopkins as a student in 1905. He was graduated with an A.B. degree in 1908 and received his M.D. degree in 1912. He was intern and assistant resident at both the Johns Hopkins Hospital and the Hospital of the Rockefeller Institute in New York from 1913 to 1917. He joined the Army Medical Corps as a lieutenant in 1917, and after two years overseas service in France and Germany was discharged with the rank of major.

He was appointed Associate in Medicine at Washington University in St. Louis that same year, and remained until 1921 when he returned to the Johns Hopkins as Associate Professor of Medicine and physician on the senior staff of the Hospital. He was appointed Assistant Dean of the School of Medicine in 1927. In 1937, he was named President of the Association of American Medical Colleges. He served as President of the Medical and Chirurgical Faculty of Maryland in 1952–53. He is a member of the American Society for Clinical Investigation, Association of American Physicians, American Society Experimental Pathology, and the Baltimore City Medical Society.

Throughout his career, Dr. Chesney has been a militant leader for the maintenance of high academic standards in medical education for both students and faculty, and for freedom from restriction, whether from government or private sources, in the conduct of the medical schools and in scientific research. Respected by his colleagues and laymen for his "instinctive courtesy and capacity to be considerate of the other's point of view," he has never hesitated to voice his opinion to doctors, legislators, and laymen alike on matters he considered important to the continued provision of high quality medical care and education.

For many years, Dr. Chesney almost single-handedly battled anti-vivisectionist activities which he declared a "serious and crippling obstacle to the advance of medical knowledge." His untiring efforts led in 1949 to a concerted stand by the doctors at the Johns Hopkins and the University of Maryland School of Medicine against the anti-vivisectionists. Following stormy public hearings before the Baltimore Board of Estimates and the Baltimore City Council, the doctors were successful in their efforts to obtain unclaimed animals, otherwise doomed to die, from the city pound. In 1950, when the anti-vivisectionists took the fight before the public on a referendum question, he was one of the founders of the Maryland Society for Medical Research, composed of leading laymen and doctors, which battled the anti-vivisectionists to an overwhelming defeat at the polls.

For many years Dr. Chesney has been a forceful and prolific writer. He published a number of scientific articles and a book, *Immunity in Syphilis,* prior to assuming the office of Dean. Since then he has written many articles for both the scientific and lay press on medical matters. He composed a play on the early history of the Hopkins entitled, *The Flowering of an Idea,* which was staged on the fiftieth anniversary of the Hospital, and a fifty-page booklet on the same occasion outlining the progress and accomplishments of the institution to that time. He is at present engaged in completing the second volume of his *The Johns Hopkins Hospital and The Johns Hopkins Uni-*

versity School of Medicine, the first volume of which was published in 1943.

Dr. Chesney is succeeded as Dean of the School of Medicine by **Philip Bard,** Professor of Physiology and Director of the Department of Physiology Dr. Bard assumed his new position on July 1. In addition to his academic and administrative responsibilities as dean, Dr. Bard will continue in his present position in the Department of Physiology.

Robert C. Disque, Dean of the Faculty and since 1933 Dean of the College of Engineering at Drexel Institute of Technology, retired on August 31st. **Harry L. Bowman,** Head of the Department of Civil Engineering and a member of the faculty since 1926, has succeeded him in both posts. Dr. Disque, who has been associated with the Institute since 1919, has been named Dean Emeritus and Professor Emeritus of Electrical Engineering. He has long been a strong advocate of the coordination of professional studies in engineering with internships in industry under what has come to be known as the Cooperative Plan of Education, which has been followed by the Drexel College of Engineering since 1919.

Alfred S. Gaskell, a design engineer for the John Deere Tractor Co. in Waterloo, Iowa, has been appointed Associate Professor of Mechanical Engineering at West Virginia University.

Warren G. Hoag, Assistant Chief of the Department of Veterinary Bacteriology for the Army Veterinary Corps in Washington, has been named Professor of Animal Pathology at Virginia Polytechnic Institute Agricultural Experiment Station.

Joseph C. Hinsey, Dean of the Cornell University Medical College and Professor of Anatomy, has resigned to accept appointment as Director of the New York Hospital-Cornell Medical Center. Dr. Hinsey will succeed **Stanhope Bayne-Jones,** for the past six years President of the Joint Administrative Board of the Center. Dr. Bayne-Jones retired on June 30th to become Civilian Technical Director of Research of the Army Medical Research and Development Program.

Francis R. Holden, formerly of the U.S. Naval Radiological Defense Laboratory, San Francisco, has joined the chemistry staff of the Stanford Research Institute. A physical chemist, he will do atmospheric research and direct some of SRI's radiological programs.

Paul E. Klopsteg, Associate Director of the National Science Foundation and a member of the Board of Directors of the AAAS, and **Elvin C. Stakman,** Emeritus Professor of Plant Pathology at the University of Minnesota and a Past President of the AAAS, will serve as official Asociation representatives at the Fourth National Conference of the U.S. National Commission for UNESCO to be held at the University of Minnesota Sept. 15–17.

The University of Wisconsin has announced the resignation of **Jesse B. Kommers,** Professor of Mechanics and Chairman of the Department of Mechanics in the College of Engineering. Dr. Kommers has been on the University's staff since 1907. In the field of engineering he is particularly well-known for his work on the fatigue of metals. He was co-author of the first book on the subject in the U.S., a book that has been translated into many languages. He is also the author of a number of other volumes on engineering, and has published many technical and research papers.

Emil Kotcher, Associate Professor of Microbiology at the University of Louisville School of Medicine has been given a leave-of-absence so that he may accept an assignment with the U.S. Public Health Service as Laboratory Director of Parasitology for the Special Technical and Economic Mission (MSA) to the Associated States of Indochina.

William A. W. Krebs, Jr. has resigned from his position as General Counsel for the National Science Foundation. **William Jay Hoff,** former assistant to the Director of the Office of Defense Mobilization and administrator of the Defense Production Administration, has been appointed to fill the vacancy.

J. Oliver Lampen, formerly Associate Professor of Microbiology at Western Reserve University Medical School, has been appointed Director of the Division of Biochemical Research at the Squibb Institute for Medical Research, New Brunswick, N. J. This group is concerned with research in nutrition, endocrinology, and general enzymatic problems.

F. Benedict Lanahan has been appointed Professor of Occupational Medicine at The Woman's Medical College of Pennsylvania. Dr. Lanahan, who became Medical Director for The Electric Storage Battery Company of Philadelphia in November, 1947, has a wide experience in industrial medicine and has specialized in lead poisoning and cardiac rehabilitation.

T. A. Lincoln, a member of the Oak Ridge National Laboratory Health Division staff since 1951, has been appointed Director of the Health Division. He replaces **J. S. Felton,** who has left the Laboratory to accept a post in the Department of Medicine and Department of Preventive Medicine at the University of Oklahoma Medical School.

Joseph J. McDonald, Professor of Surgery at the Columbia University College of Physicians and Surgeons, has been appointed Dean of the medical school at the American University of Beirut. He succeeds Norman B. Nelson, who has resigned to become Dean of the medical school of the State University of Iowa (News and Notes, March 6). Dr. McDonald had previously served four years at Beirut.

William L. Madison has been appointed Manager of the Pharmaceutical Development Department of McNeil Laboratories, Philadelphia.

Carl Marks, President of the recently established Epilepsy Association of New York, has announced the appointment of **Harry Sands** as Executive Director. Formerly a faculty member of both New York University and Brooklyn College, Dr. Sands has served also as Director of the Committee for Public Understanding of Epilepsy.

Education

Three new research instruments—a wind tunnel, small water tunnel, and hydraulic system—are nearing completion at the **Pennsylvania State College.** The three will be used with the Garfield Thomas Water Tunnel. This giant tunnel, completed more than three years ago, is a testing instrument of the Ordnance Research Laboratory, and is used to study torpedo propeller-body systems. The new facilities not only will aid in this propeller research program, but also will permit important basic research in fluid mechanics. While the use of a wind tunnel to study hydraulic problems is a relatively new development, there are many advantages to using air instead of water as a testing fluid. Even in the study of cavitation effects, air studies are useful in evaluating cavitation potentialities. The wind tunnel also will be used for conducting pilot studies of various water tunnel problems and will make it possible to conduct these studies at less cost than if the large tunnel had to be used.

The **Rochester Institute of Technology** has been granted approval to conduct courses leading to the bachelor of science degree. Although details have not been completed, it is expected that students entering R.I.T. in the fall of 1953 will be able to continue study toward a bachelor's degree if they so desire.

The **University of Wisconsin** Board of Regents has approved a contract between the University and the governments of the U.S. and India, under which as many as 16 American engineering and technical educators will be sent to India during the next two years to help improve the engineering colleges of that nation. Total cost of the two-year program is not to exceed $680,000, all given to the UW by the U.S. Government through its Technical Cooperation Administration of the Point Four program. Under terms of the contract, the UW will establish an inter-university cooperative relationship with 7 engineering and technical colleges and institutes in India to aid them through a program to improve, strengthen, and expand the technical educational capacities of the Indian schools. The schools are the Bengal Engineering College of Sibpur, West Bengal; the Indian Institute of Science at Bangalore, Mysore; the College of Engineering and Technology at Jadavpur, Bengal; the Indian School of Mines at Dhanbad, Bihar; the Birla Engineering College at Philani, Rajasthan; the Mechanical and Electrical Engineering College at Sindri, Bihar; and the Roerkee University at Roerkee, Uttar Pradish.

Grants and Fellowships

The following **AAAS Research Grants** have been awarded:

R. B. Channell, Duke University, for his research project "Revisional Study of the Genus Marshallia."

Tom Daggy, Davidson College, for his research project "Survey of Microarthropods of Forest Soil and Litter."

Everett O. D. Tuneberg, North Dakota School of Forestry, for his research project "Utilization of Aspen in the Turtle Mountains."

The **American Heart Association** has marked its fifth anniversary as a voluntary health agency by awarding, jointly with its affiliates, an additional $473,930.59 for 89 research grants-in-aid in the field of heart and blood-vessel diseases. The latest awards increase to a grand total of almost $6,500,000 the sums spent for research studies by the American Heart Association and its affiliated state and local associations over the five-year period.

Applications are now being accepted for research awards to be made during the coming year. Applications for Research Fellowships and Established Investigatorships should be sent to the Association *by Sept. 15,* and applications for Research Grants-in-Aid should be filed *no later than Dec. 1.* Information and forms may be obtained from the Medical Director, American Heart Association, 44 E. 23rd St., New York 10, N.Y. The applications will be reviewed by the Research Committee of the Scientific Council. Established Investigatorships, which may be extended annually for a five-year period, range from $6,000 to $9,000. They are available to scientists of proven ability who are engaged in a research career. Research Fellowships, awarded for a one-year period, range from $3,500 to $5,500, and are open to persons interested in research and in an academic career. Grants-in-aid are of various amounts, usually not exceeding $10,000. They are made on the basis of specific, acceptable projects to experienced investigators working in non-profit institutions, medical schools, hospitals and laboratories, who have demonstrated their productiveness, or who otherwise give promise of accumulating useful new information.

The **Commonwealth Fund Fellows** who will be pursuing advanced scientific studies in the United States during the coming academic year are as follows:

General Fellowships

William Gilbert Chaloner, Demonstrator in Botany, Reading. To study paleobotany at Michigan.

Ronald James Gillespie, Lecturer in Chemistry, Unviersity College, London. To study the theory and experimental measurement of the dielectric properties of polar solids and liquids at Brown.

Hans Leo Kornberg, Research Fellow, Sheffield. To study biochemistry (the turnover of the 6-amino group at ATP) at Yale.

Peter Gerald Moore, Assistant Lecturer in Statistics, University College, London. To study the application of statistical methods to biology and ecology at Princeton.

Edwin Albert Power, Assistant Lecturer in Mathematics, University College, London. To investigate the property and behavior of mesons artifically produced by high energy particle accelerators at Cornell.

Geoffrey Colin Shephard, Lecturer in Mathematics, Bir-

mingham. To study modern algebraic geometry and abstract algebra at Princeton.

Roger John Tayler, research student, Clare College, Cambridge. To study theoretical astrophysics and observational astronomy at Princeton.

Raymond Lloyd Williams, St. John's College, Oxford. To undertake research in infra-red spectroscopy at the University of California, Berkeley.

Home Civil Service Fellowships

Benjamin Richard Feaver, District Forest Officer, Aberdeen, Scotland. To investigate the mechanization of forestry operations in the U. S., under the guidance of the U. S. Department of Agriculture's Forest Servcie.

Dominion Civil Service Fellowships

Henri Pieter Albert DeBoom, Lecturer in Embryology and Comparative Anatomy of Domestic Animals, University of Praetoria, South Africa. To study comparative anatomy at Cornell.

Colonial Civil Service Fellowships

Francis Alfred Loyd, District Officer, Provincial Administration, Fort Hall, Kenya Colony. To investigate the techniques and methods of planning, in relation to natural resources.

Colin Stokes Ramage, Acting Assistant Director, Royal Observatory, Hong Kong. To study tropical and sub-tropical meteorology, probably at Florida and Chicago.

Fellowships through the Salzburg Seminar in American Studies.

Kjell Ando Romanus Fastborg, Psychiatric Resident, Caroline Institute, Stockholm. To study psychiatry and sociology at Yale.

Robert Charles Pages, Attaché, Centre National de la Recherche Scientifique, Paris. To study psychology at Harvard.

1953–54 Second Year Extensions, General

Victor Kurt Alfred Morris Gugenheim, Fellow, Magdalen College, Oxford. To study mathematics at Princeton for 9 months.

Hugh Esmor Huxley, research student in Medical Research Council unit. Cavendish Laboratory, Cambridge. To study the molecular structure of muscle and the mechanism of muscular contraction at the Massachusetts Institute of Technology for 9 months.

Nicholas Avrion Mitchison, Fellow, Magdalen College, Oxford. To study the genetics of microorganisms, especially the metabolism of antigens at the Jackson Memorial Laboratory, Bar Harbor, Maine, for 9 months.

Derek Reginald Higham Phillips, postgraduate student, Liverpool. To investigate the uses of natural illumination in urban planning and building at the University of California, Berkeley, for 9 months.

Alan John Weir, Jesus College, Cambridge. To investigate problems connected with Lie algebras and group theories at Princeton for 9 months.

Dominion

Edmund John Buchanan Foxcroft, Principal Executive Officer and Executive Member, National Security Resources Board, Prime Minister's Department, Canberra, A.C.T. To study the economics of natural resources at Harvard and in Washington, D. C., for 6 months.

Henrietta Crawford Kirkwood, Post-primary School Inspector, Education Dept., Government of New Zealand. To study family relations and child development at Teacher's College (Columbia) for 9 months.

Jack Neville Lewis, Acting Principal Research Officer (Economic Policy), Bur. of Agricultural Economics, Dept. of Commerce and Agriculture, Canberra. To study agricultural economics at Littauer Center, Harvard, for 9 months.

Salzburg

Peter Max Atteslander, Secy., Swiss Comm. of World University Service, Zurich. To study industrial sociology at Cornell for 9 months.

The Rockefeller Foundation has made a grant of $100,000 to the University of Washington, Seattle, for researches in protein chemistry under the direction of Hans Neurath, Professor of Biochemistry. The grant became effective July 1 for a 7-year period.

Meetings and Elections

The Illuminating Engineering Society has elected the following officers for 1953–54: president, A. H. Manwaring, Philadelphia Electrical & Manufacturing Company, Philadelphia; vice president, R. F. Hartenstein, Ohio Edison Company, Akron; general secretary, M. N. Waterman, Westinghouse Lamp Division, Bloomfield, N. J.; treasurer (by re-election), Kirk M. Reid, General Electric Company, Cleveland, Ohio; vice president (2nd year of 2-year term), D. M. Jones, Curtis Lighting of Canada, Ltd.

The Sixth International Congress for Microbiology will be held in Rome, Sept. 6–12. On the Organizing Committee for the Congress were included: president, V. Puntoni; vice presidents, L. Califano, G. Penso, and P. Redaelli; secretary-general, E. Biocca; treasurer, M. Pantaleoni; and I. Altara, C. Arnaudi, G. A. Canaperia, G. Caronia, V. Cilli, A. Cimmino, D. Marotta, A. Morelli, B. Polettini, C. Sibilia, and A. Zironi. The work of the Congress will be divided, as has been customary, into a large number of sections covering different branches of microbiology. Six symposia have also been arranged and give promise of being of very general interest. The subjects of the symposia, and the organizers thereof, are: Bacterial Cytology (S. Mudd and G. Penso); Microbial Metabolism (E. B. Chain); Nutrition and Growth Factors (W. H. Schopfer and D. D. Woods); Morphology, Biology, and Systematics of Actinomycetales (E. Baldacci and P. Redaelli); Growth Inhibition and Chemotherapy (H. Eagle and E. B. Chain); and Interaction of Viruses and Cells (F. C. Bawden and G. Penso). Papers contributed to the symposia are being printed in book form to be ready for distribution at the opening session of the Congress. This will be a highly commendable achievement, especially in view of the fact that publication of the proceedings of many of the post-war international congresses has been regrettably slow. Prior publication of papers contributed to a symposium should certainly make for a better discussion at its sessions.

"The Research Report—Its Functions, Preparation, Distribution and Use," will be the topic for a full-day symposium before the Division of Chemical Literature at the American Chemical Society's 124th National Meeting in Chicago on Sept. 8. The program will include discussions of less obvious uses of the research report as well as of its primary function in communicating laboratory research results to administrative, sales, patent, and other departments. The problem of effective distribution in various types of organizations and the handling of reports under security restrictions will be treated by speakers from both industry and government. Of particular interest to the research man who must prepare reports are discussions of the content, style, and form best suited to the purpose.

Miscellaneous

The European Prize Cortina-Ulisse is a one million lire prize awarded annually to a scientific publication. It has been promoted by the magazine *Ulisse* of Rome, edited by Maria Luisa Astaldi. The 1953 prize is organized in cooperation with the Italian National Productivity Center, and will be for a work concerning economic and social sciences specifically dealing with productivity. Only works printed for the first time in Europe during the last five years will be considered. Works must be submitted in triplicate in French, German, or English either by the author or by the publisher to The Editor, Rivista Ulisse (Sezione Premio Europeo Cortina-Ulisse), 43 Corso d'Italia, Rome, Italy, *before midnight, October 31, 1953.*

The U.S. National Museum, Smithsonian Institution, has opened its first **exhibit of antibiotics,** in observance of the 25th anniversary this year of the discovery of penicillin. The exhibit was assembled by George Griffenhagen, associate curator of the Museum's division of medicine and public health, and is located in the Smithsonian's Arts and Industries Building.

A Human Engineering Section has been established in the Office of Naval Research, Washington, as a result of a recent study of the current activity in this field within the Navy. One important fact disclosed by the study is that only 7% of all Navy man-machine systems which require human engineering attention are receiving it, due partly to the gap that exists between research results and the applications of those results to equipment design. A limited number of copies of the official report are available from the Human Engineering Section, Office of Naval Research, Code 454H, Washington 25, D.C.

The **Museum of Northern Arizona at** Flagstaff will celebrate its 25th anniversary on August 22. In addition to speakers, there will be an inspection of buildings and laboratories, including the new Research Center now under construction.

The **U.S. Geological Survey's "Progress Report on Investigations of Western Phosphate Deposits"** is now available to the public. The report is being placed on open-file now, in advance of publication, to make information available for use in connection with the search for new deposits during the current field season. Copies of the preliminary manuscript may be inspected at the Idaho Bureau of Mines and Geology, Moscow, Idaho, and at the following offices of the Geological Survey: Room 1033 General Services Building (Library), Washington, D.C.; Public Inquiries Office, Room 468, New Custom House, Denver, Colo.; South 157 Howard St., Spokane, Wash.; Public Inquiries Office, Room 504, Federal Bldg., Salt Lake City, Utah; and Montpelier, Idaho.

Recent Deaths

Homer Addams (80), heating and ventilating engineer, Philadelphia, Pa., July 3; **Raymond C. Bacon** (45), research scientist, Oak Ridge, Tenn., July 7; **Albert L. Baker** (56), electrical engineer, New York, N. Y., May 4; **Philip Walter Berg** (35), entomologist and professor, Lafayette, Ind., April 14; **Guido Bergamo** (59), physician and radiologist, Venice, Italy, June 26; **Solon S. Bernstein** (56), internist, New York, N. Y., July 10; **Erwin Brand** (62), biochemist and professor, Hastings-on-Hudson, N. Y., July 12; **Karl Bremer** (68), South African Minister of Health, Capetown, South Africa, July 18; **Marion Luther Brittain** (87), president emeritus of Georgia Institute of Technology, Atlanta, Ga., July 1; **May Ayres Burgess** (65), nursing expert and educator, Washington, D. C., July 15; **Willoughby M. Cady** (46), physicist, Pasadena, Calif., June 29; **Edward G. Carey** (75), maritime engineer, Plainfied, N. J., June 29; **Philip Howard Cobb** (72), chemist and professor, Portland, Me., July 18; **William C. Coker** (80), botanist and professor emeritus, Chapel Hill, N. C., June 27; **Cole Coolidge** (56), research chemist, Wilmington, Del., July 11; **Early C. Eastman,** chemical engineer, Westfield, N. J., July 12; **Joseph Echtman** (67), specialist in cardiology and physical medicine, New York, N. Y., June 26; **Bolivar Lang Falconer** (82), mathematician, Marlin, Texas, April 26; **William L. Finley** (76), naturalist, Portland, Ore., June 29; **Newell T. Gordon** (63), lighting scientist, Schenectady, N. Y., July 18; **Harry A. Hamilton** (50), mechanical engineer, Fanwood, N. J., July 9; **John W. Hoffman** (85), educator, San Marino, Calif., July 3; **John Benjamin Holland** (43), sociologist and professor, Havana, Cuba, June 29; **Henry W. Jeffers, Sr.** (82), agriculturist and dairy expert. Plainsboro, N. J., July 17; **Frank Howard Lahey** (73), surgeon and founder of the Lahey Clinic, Boston, Mass., June 27; **Margaret C. Lewis** (83), physician, Philadelphia, Pa., July 13; **Joseph J. Lukacs** (45), electrical engineer, New Rochelle, N. Y., July 15; **William H. McCastline** (77), physician and professor, Brandon, Vt., July 11; **Arthur Coleman Monahan** (76), aviation editor of Science Service, Washington, D. C., July 2; **Muriel P. Munro,** research chemist, Philadelphia, Pa., July 12; **E. George Payne** (75), dean emeritus of New York University School of Education, Cushing, Me., June 28; **Clara Reimel** (81), physician, Philadelphia, Pa., June 30.

Col. Myron Rudolph (64), specialist in preventive medicine, Washington, D. C., June 30; **Frank L. Seymour-Jones** (57), research chemist, Englewood, N. J., July 2; **Frank E. Stevenson** (57), pediatrician and professor, Cincinnati, Ohio, July 9; **Davis H. Tuck** (64), consulting and electrical engineer, Redding, Conn., July 5; **Richard von Mises** (70), mathematician and professor, Boston, Mass., July 14; **Theodore Whittelsey, Sr.** (85), industrial chemist, Philadelphia, Pa., June 26.

Technical Papers

A Criticism of the Indiscriminate Use of the Schmidt-Thannhauser Method for the Fractionation of Nucleic Acids in Biological Material

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Interest in the nucleic acids from a variety of tissues is being displayed by an increasing number of biologists. Many who would not consider themselves well versed in biochemical procedures are attracted to the Schmidt-Thannhauser (*1*) method of separation and determination because of its relative simplicity when compared with other methods. The chief attraction of this method is that it can be followed by only one type of determination (i.e., phosphorus) rather than by the two or more methods necessary when the sugar moieties of the nucleic acids are used as the basis for analysis. It has become customary among many biologists to accept without question the general applicability of this method. It is the purpose of this communication to point out and emphasize to biologists some of the hazards inherent in this method.

The Schmidt-Thannhauser method of separation of ribonucleic acid (RNA) from deoxyribonucleic acid (DNA) rests upon the claim of Steudal and Peiser (*2*) that RNA is quantitatively hydrolyzed to acid-soluble nucleotides by treatment with 0.75 *N* NaOH at room temperature in 24 hr, whereas DNA resists this treatment and remains completely precipitable by mineral acid. According to the theories of Fonó (*3*), Brown and Todd (*4*), and Markham and Smith (*5*), the difference between these two nucleic acids in their susceptibility to alkaline hydrolysis is due to the formation by RNA of highly alkali-labile "cyclic" nucleotides by esterification of the free —OH group on the 2′or 3′ carbon atom of ribose. Deoxyribose has no corresponding —OH group, and so DNA is incapable of forming such "cyclic" nucleotides and therefore can not be degraded in this manner. In the usual Schmidt-Thannhauser methods, the material to be analyzed is incubated at 37° C for a period of from 18 hr to three days with 1 *N* KOH, 1 *N* NaOH, or 0.3 *N* NaOH. At the end of this incubation period, DNA is precipitated by the addition of suitable amounts of mineral acid. It is then assumed that all the DNA is precipitated and that all the RNA remains in the supernatant fluid. Phosphorus determinations on the supernatant fluid (after adjustment for any phosphoproteins) are considered an estimate of RNA and the phosphorus content of the precipitate after hydrolysis is considered an estimate of DNA.

Assuming for the moment that the separation of these acids by such a procedure is adequate, the use of phosphorus determinations as a means of estimating these nucleic acids is itself fraught with many dangers, the most obvious of which are: (1) the danger of contamination of one fraction with phosphorus-containing compounds from another fraction, (2) the possibility of differential extraction and/or precipitation of phosphorus and the sugar moieties, and (3) the inadequacy of the general assumption of a constant percentage of phosphorus in the nucleic acid derivatives. Schneider (*6*) made a detailed comparison of the results yielded by the Schmidt-Thannhauser method and his own method (*7*) which depends upon the simultaneous extraction of both types of nucleic acids with hot trichloroacetic acid (TCA). RNA and DNA are determined by estimation of ribose and deoxyribose in portions of this extract. In the particular tissues which Schneider (*6*) used for comparison good agreement between the two methods was obtained.

Evidence is accumulating in the literature that there may be serious discrepancies in results obtained by the two methods. These discrepancies obviously are not due to errors produced by the use of phosphorus determinations alone (contaminations, differences in phosphorus composition, etc.) but are more likely due to the inadequacy of the actual separation in the Schmidt-Thannhauser method. Davidson (*8*) noted that the use of the Schmidt-Thannhauser technique gave, for several tissues, higher ratios of ribonucleic acid phosphorus to deoxyribonucleic acid phosphorus than other methods. Davidson, Frazer, and Hutchinson (*9*) showed that the total phosphorus of a Schneider extract from a rabbit liver homogenate contained onyl 75% of the phosphorus found in the fractions corresponding to the DNA and RNA of a Schmidt-Thannhauser hydrolyzate. They suggested that the Schneider procedure did not split off all the nucleic acid phosphorus and they showed that about 25% of this Schneider residue, if subjected to Schmidt-Thannhauser procedure, is alkali-soluble. Of this soluble material, about 85% is acid-soluble organic phosphorus, but it was not shown that this fraction contained ribose. More recently, Mauritzen, Roy, and Stedman (*10*) have shown specifically that, in a Schmidt-Thannhauser fractionation of thymus nuclei, a significant amount of degraded DNA appears in the acid supernatant fluid ("RNA fraction"). The general validity of the basic assumption of Steudel and Peiser (*2*) is thereby called in question. Either the material taken for analysis contains some DNA already in a sufficiently degraded state to be soluble in alkali or, contrary to Steudel and Peiser, some DNA can be hydrolyzed by treatment with alkali. Most recently,

[1] This investigation was supported in part by a research grant C-1074 (C2) M and G from the National Cancer Institute of the National Institutes of Health, Public Health Service.

[2] The author is deeply grateful to Dr. Charity Waymouth for her numerous helpful suggestions and criticisms in the preparation of this manuscript.

TABLE 1

COMPARISON OF SCHMIDT-THANNHAUSER AND SCHNEIDER METHODS ON MAMMARY TUMOR TISSUE
Results expressed as μg/mg dry tissue

Tissue sample*	Total phosphorus†		Ribonucleic acid (RNA)‡			Deoxyribonucleic acid (DNA)§			Residual phosphorus
	Schmidt-Thann. alk. hydrol.	Schneider TCA extract	Phos. on Schmidt-Thann. supern.	Orcine on Schmidt-Thann. supern.‖	Orcine on Schneider extract	Phos. on Schmidt-Thann. ppt.	Diphenylamine on Schmidt-Thann. ppt.	Diphenylamine on Schneider extract	Schneider residue
1									
A	13.3	10.6	7.9	49.6	44.1	5.0#	45.8#	76.6	1.1
B	12.3	11.1	7.6	47.6	41.5	5.2**	48.1**	66.4	0.5
2									
A	7.4	7.3	4.3	29.2	36.6	2.5#	26.5#	52.8	0.0
B	8.1	8.1	4.2	30.0	37.0	4.1**	40.9**	52.4	0.0
3									
A	12.7	11.5	10.4	33.8	37.6	2.1#	25.7#	103.0	1.2
B	11.7	12.1	10.0	31.6	38.8	1.9**	32.0**	110.8	1.3

* Samples 1, 2 and 3 were from mammary tumors of different stages of development.
** Schmidt-Thannhauser precipitate hydrolyzed with NaOH.
† Phosphorus determined by the method of Fiske and SubbaRow (modified) (*17*).
‡ RNA determined by the Mejbaum (*13*) orcinol method.
§ DNA determined by the Dische (*15*) diphenylamine method.
‖ Average of two determinations.
Schmidt-Thannhauser precipitate extracted with hot trichloroacetic acid (in sample 2A, extraction was short and did not extract all of the DNA from the precipitate).

McIndoe and Davidson (*11*), working with free nuclei, have found that by dissolving and reprecipitating several times the original Schmidt-Thannhauser precipitate, the DNA which was originally precipitatable tended to become degraded and alkali-soluble. Such a finding makes some of the longer incubation periods used by some workers highly suspect. Furthermore, it has been shown by Davidson and Smellie (*12*) that the ribonucleotide fraction derived by a modified Schmidt-Thannhauser separation from rat liver homogenate contains at least five other organic phosphate components. Ribonucleotides contribute only 75% of the total phosphorus of this fraction. Only one of the contaminating components (*A*) which could be separated ionophoretically from the nucleotides has a detectable absorption in the ultraviolet. The principal contaminants in this case are not deoxyribonucleotides. These observations emphasize the great caution that should be exercised before it is assumed that the "RNA fraction" from any unknown material contains only ribonucleotides.

Data collected in the course of another investigation support the finding of Mauritzen, Roy, and Stedman (*10*) that in certain tissues DNA, either because it is less polymerized or because it is less resistant to alkaline hydrolysis, is not completely precipitated by acidification after initial incubation with 1 *N* NaOH. Mammary tumor tissue from C3H mice was analyzed by both Schmidt-Thannhauser and Schneider methods (Table 1). It is clear that an appreciable portion of the DNA is *not* precipitated upon acidification of the Schmidt-Thannhauser alkaline hydrolyzate. Short-

TABLE 2

APPARENT DIFFERENCES IN PHOSPHORUS AND SUGAR CONTENTS OF NUCLEIC ACIDS OF MAMMARY TUMOR TISSUE WHEN ANALYZED BY THE SCHMIDT-THANNHAUSER AND SCHNEIDER METHODS
Results expressed as μg/mg dry tissue

Tissue sample*	Method	Ribonucleic acid fraction (RNA)				Deoxyribonucleic acid fraction (DNA)			Total phosphorus		
		Time of alkaline hydrol.	Supernat. phos.	RNA in supernat. orcine†	RNA in TCA extr. orcine	Phos. on ppt.	DNA in ppt. diphenylamine†	DNA in TCA extr. diphenylamine	Phos. in alk. hydrol.	Phos. in TCA ext.	Calc. from orcine and diphenylamine‡
A	Schmidt-Thann.	4 hr	8.2	42.6	.....	3.6	47.7	.....	11.2	.....	8.7
B	Schmidt-Thann.	24 hr	8.8	38.2	.....	2.9	36.4	.....	11.3	.....	7.2
C	Schneider	.....	.....	.....	49.3	.....	.....	101.3	.....	12.2	14.8
D	Schneider	.....	.....	.....	53.5	.....	.....	104.9	.....	10.7	15.4

* All tissue samples were from the same initial homogenate.
† Average of two determinations.
‡ Calculated on the basis of 9.8% phosphorus in DNA and 9.5% phosphorus in RNA.

ening the period of hydrolysis has no effect on the amount of DNA precipitated (Table 2). This could be taken to support the interpretation that the degraded part of the DNA fraction is already in the alkali-soluble form before the material is treated with alkali. This finding does not necessarily contradict the finding of McIndoe and Davidson (*11*) that the repeated reprecipitation of DNA from isolated nuclei results in increasing degradation of the DNA which was at first precipitable.

It can be seen from Table 2 that there are some discrepancies between the total extractable phosphorus values given by direct phosphorus analysis and the amounts calculated on the basis of theoretical phosphorus contents of 9.8% and 9.5% for DNA and RNA respectively (Schneider, *7*). These can probably be accounted for on the basis of (a) a slight interference in the Mejbaum (*13*) orcinol reaction by DNA (von Euler and Hahn, *14*) and (b) high values on the Dische (*15*) diphenylamine reaction in the presence of protein (Dounce, *16*). In the experiments reported here, the standard solutions of nucleic acids used for calibration were made up in solvents of exactly the same composition as those used in the unknowns and were varied to correspond to the method of extraction or fractionation.

Data similar to those reported here have been obtained on occasion from mouse liver and from old mouse uterine tissue. It is suggested that, before the Schmidt-Thannhauser method is used as a method for the determination of DNA and RNA, a check should be made with another method to find out whether effective separation is achieved in the particular tissue being studied. Acid precipitation after alkaline hydrolysis of suitably prepared nucleic acid-containing tissue homogenates does not always result in complete separation of the deoxyribonucleic acids. For this reason, and because the acid-soluble fraction may also contain non-nucleotide organic phosphorus, it is unsafe to use phosphorus estimations on the acid-soluble and acid-insoluble fractions as the sole means of distinguishing the DNA and RNA.

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The Occurrence of Acquired Hemolytic Anemia in Subjects of Blood Group O

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In a previous study of the blood groups of 26 patients suffering from hemolytic anemia (*1*), there was noted a slight increase in the incidence of blood group O. To investigate this trend in a larger sample, the blood groups of 58 subjects of hemolytic anemia were analyzed in relation to the type of hemolytic anemia involved, i.e., congenital or acquired.

Of the 58 cases of hemolytic anemia studied, 31 were diagnosed as congenital hemolytic anemia, and 27 as acquired hemolytic anemia. The diagnoses were made by competent hematologists and were verified by frequent references to the progress of the individual cases. All the patients who had acquired hemolytic anemia were unrelated; of those with congenital hemolytic anemia, 7 were members of 3 families (two instances of a father and daughter, and one of a father, daughter, and granddaughter), and the rest were unrelated.

In Table 1, the ABO blood group distribution among subjects of hemolytic anemia is presented, and the preponderance of group O among those with acquired hemolytic anemia is evident. The distribution of ABO blood groups in the 58 subjects of hemolytic anemia was compared with the normal distribution of the ABO blood groups in an unselected, white, population.

There was found to be a statistically significant increase in the incidence of blood group O among patients with acquired hemolytic anemia, whereas no significant deviation from the expected distribution of ABO blood groups occurred among patients with congenital hemolytic anemia.

TABLE 1

THE DISTRIBUTION OF ABO BLOOD GROUPS IN 58 PATIENTS WITH HEMOLYTIC ANEMIA

Type of hemolytic anemia	Total No.	%	ABO blood groups							
			O (N = 45%) (2)		A (N = 41%)		B (N = 10%)		AB (N = 4%)	
			No.	%	No.	%	No.	%	No.	%
All types total	58	100	36	62.1	13	22.4	9	15.5	0	0
Congenital	31	100	15	48.4	11	35.5	5	16.1	0	0
Acquired	27	100	21	77.8	2	7.4	4	14.8	0	0

The distribution of ABO blood groups among patients afflicted with *acquired hemolytic anemia* was found to parallel closely the distribution of ABO blood groups among individuals who are *non-secretors of type A group-specific substance*. Preliminary experiments in our laboratory have indicated a possibility that susceptibility to acquired hemoyltic anemia may be related to the status of nonsecretion of type A group-specific substance.

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Small-Volume Dosimeter for X-Rays and Gamma-Rays

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A new system of x-ray and gamma-ray dosimetry for the monitoring of personnel exposed to A-bomb attack was proposed at this laboratory in 1947 and has since been described in a number of publications (*1–3*). This method of dosimetry employs the phenomenon of radiophotoluminescence (*4*), which may be defined as the creation of new, stable luminescent centers in a material by the photochemical action of ionizing radiations. Before exposure to such radiations, an ideal radiophotoluminescent material is nonluminescent under ultraviolet light; after exposure to ionizing radiations, it can be repeatedly or continuously excited to luminescence by ultraviolet light. It has been shown (*2, 3, 5*) that the luminescence intensity of a radiophotoluminescent material, under fixed conditions of ultraviolet light illumination, is proportional to the dosage of ionizing radiation to which the material has been exposed. Visual or photoelectric means may be used for measuring this luminescence and interpreting it in terms of dosage. Of the many synthetic materials found that show this effect (*5, 6*), the one selected as most economical and practical for large-scale manufacture was a silver-activated phosphate glass (*1–3, 5, 6*). This glass, prior to treatment with ionizing radiations, is almost devoid of luminescence under 3650A excitation; after x-ray or gamma-ray exposure, 3650A excitation produces an orange luminescence. The undosed glass retains its sensitivity to ionizing radiations apparently indefinitely, and the dosed glass retains its ability to luminesce under ultraviolet excitation for at least many months when stored in the dark. The response of the glass is linear with dosage, cumulative, and independent of dose rate over a wide range of dose rates. The temperature at which the dose is delivered has a measurable effect on the yield of luminescence centers, and the temperature at the time of measurement of the luminescence of the glass likewise has an effect on the intensity of luminescence. Both temperature effects are comparatively small and can be taken into account in estimating the dosage from the luminescence intensity.

With a $1 \times 1 \times 0.1$-cm plate of the sensitive glass, used in conjunction with a 100-watt C-H4 ultraviolet lamp and a photomultiplier tube, one can detect the luminescent centers produced by as little as 10R of radium gamma-rays (*2, 3*). In the dosimeter adopted for use by the U. S. Navy (*7*), a $\frac{3}{4} \times \frac{3}{4} \times 3/16$-in. rectangular parallelopiped of the glass is used as the sensitive element. With this larger block of glass it is easier to detect the fluorescence, hence the Navy instrument for measuring the brightness and interpreting it in terms of dosage contains a small 4-watt ultraviolet lamp (Type RP-12) instead of a 100-watt source.

In connection with radiation injury studies on small animals being conducted by the Biology Department, Boston University, it became of interest to explore the feasibility of reducing the size of the sensitive glass element, so that it might be possible to implant it in body tissue. This note presents the results of preliminary efforts toward such size reduction.

Although fine filaments of the glass, of the order of 0.20 mm diameter, gave a strong fluorescence after a dose of approximately 100 roentgens of soft (110 kvp) x-rays on visual inspection under a 100-watt C-H4 "blacklight" lamp, it was decided that specimens of somewhat larger size would be more suitable for measurement in a photoelectric fluorometer. A rod 1 mm in diameter and 6 mm in length was considered to be of satisfactory size. Random lengths of such rods, with diameters between 0.95 and 1.05 mm, were cut to proper length and the end terminations polished.[1]

A photoelectric fluorometer, shown schematically in Fig. 1, and basically identical with the fluorometers previously described (*2, 3, 7*), was constructed to accommodate the rods. A rod, held in any one of the holes in a movable slide, can be interposed between the 100-watt C-H4 ultraviolet lamp and the 1P21 photomultiplier tube, in such a way that the ultraviolet radiation impinges on the rod normal to its axis, while the photomultiplier collects fluorescent light emitted through one of the flat ends of the rod. Visible light from the lamp itself is excluded by an ultraviolet transmitting filter such as Corning 9863 placed between the lamp and the glass rod. Scattered ultraviolet light is excluded from the photomultiplier by an orange filter placed between it and the glass. Variable high voltage for the photomultiplier is provided by a regulated power supply or by batteries, and the photomultiplier current is measured with a suitable galvanometer.

[1] The glass rods were provided through the courtesy of Warren Beck, of the Minnesota Mining and Manufacturing Company, and Norbert Kreidl and Gerald Blair, of the Bausch & Lomb Optical Company.

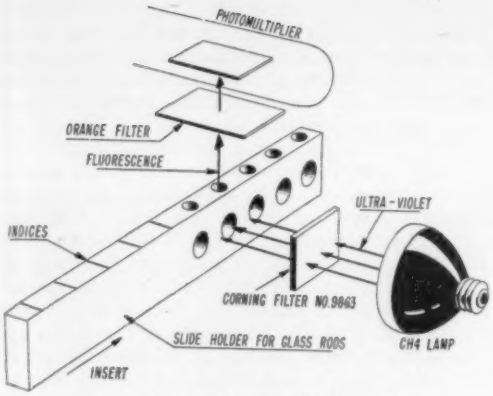

FIG. 1. Schematic diagram of fluorometer.

Since the reading obtained from any rod will depend on the ultraviolet light intensity and on the photomultiplier voltage, the fluorescence of an "unknown" specimen is always compared to that of a "standard" rod, i.e., a rod that has been exposed to a known dosage. Some light is detected by the photomultiplier even with an undosed rod, due either to the fluorescence of trace impurities in the glass or to other causes. The reading obtained with an undosed rod (the "predose fluorescence") must, therefore, always be subtracted from all other readings. The sliding rod holder with five holes makes it possible to load the instrument with three "unknown" rods, the "standard" rod, and an undosed rod, and read them all in quick succession. Somewhat more reproducible results are obtained, however, if the various rods are mounted in sequence in the same positioning hole.

The linearity of response of the silver-activated phosphate glass in the rod configuration is shown in Fig. 2. To obtain the data in this figure, rods were irradiated with 220 kvp x-rays in a direction perpendicular to their axes, the dosage being measured with a Victoreen r-meter. Three rods were exposed to each dosage indicated in the figure, and measured in the fluorometer in the above-described fashion. Due to the limited amount of glass available, the effect of orientation of the rods with respect to the direction of the x-ray beam was not explored.

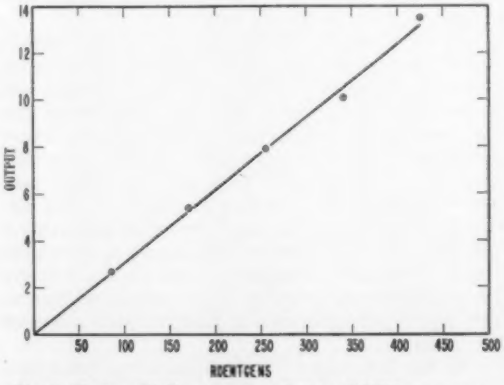

FIG. 2. Photomultiplier output vs dosage of 220-kvp x-rays.

It has been previously shown (*3*) that the response of the silver-activated phosphate glass in other sizes and configurations is strongly energy-dependent. The energy-dependence of the glass was redetermined for the millimeter-rod configuration through the courtesy of F. H. Attix, Radiation Laboratory of the National Bureau of Standards, who exposed pairs of the rods to Co^{60} radiation (average energy = 1.2 mev) and to various effective lower energies from a constant potential x-ray machine. The data obtained, shown in Fig. 3, is quite similar to the earlier results, but the ratio of peak sensitivity to sensitivity at 1.2 mev is approximately 35% greater with the rods. The sensitivity of the rods to Co^{60} radiation is approximately one twenty-fifth of their sensitivity to 70 kev x-rays.

Typical values of the photocurrents observed with 800 volts applied to the photomultiplier are: 0.03 μamp for an undosed rod; 0.83 μamp for a rod dosed with 100 roentgens of 70 kev x-rays; and 0.06 μamps for a rod dosed with 100 roentgens of Co^{60} gamma-rays. For x-rays of energies near 70 kev, to which the glass is most sensitive, the "predose" fluorescence is thus equivalent to the fluorescence increment produced by a 4-roentgen dose. For the more penetrating radiations of about 300 kev and higher, the "predose" fluorescence is equivalent to the fluorescence increment produced by a 100-roentgen dose. The "predose" fluorescence can be measured with a precision of ±10%. Dosages producing about ten times the "predose" fluorescence can be determined with a precision of ±5%, while dosages that produce a fluorescence increment equal to or lower than the "predose" fluorescence may be measured with correspondingly poorer precision. Factors contributing to the errors of measurement include the presence of imperfections in the glass rods, such as small bubbles, cracks, striae, and scratches on the end faces, and play in the mechanics of the fluorometer, which may permit small variations in the positioning of the rods with respect to the ultra-

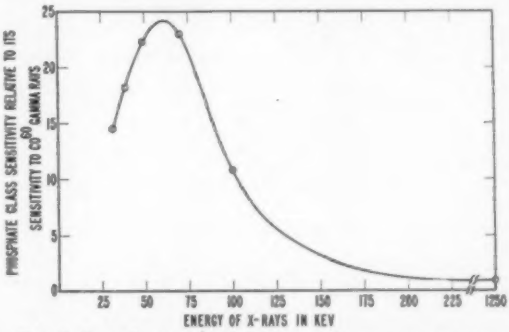

FIG. 3. Dependence of sensitivity of rods on x-ray energy.

violet source and the photomultiplier. Improvements in the quality of the glass rods and in the mechanism for positioning them may be expected to increase the precision of measurement.

The energy dependence of the silver-activated phosphate glass appears to be a limitation on it use for *in vivo* dosimetry. The seriousness of this limitation can be more clearly assessed after the completion of depth dose experiments now in progress. The possibility exists that proper shielding can be devised for the rods which will minimize their energy dependence. Such shielding has already successfully reduced the energy dependence of larger rectangular blocks of glass to ±20% over the range 0.08–1.2 mev (*3, 7*). For problems in dosimetry where the energy dependence of the glass does not interfere, considerable advantages may be offered by the small size of the rods and the other excellent features of the radiophotoluminescent system of dosimetry.

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The Tetrazolium Test for Dormancy and Germinability of Gladiolus Cormels

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The need for a rapid method of estimating dormancy in gladiolus cormels has led to the adaptation for this purpose of the tetrazolium method for testing germinability of seeds (*1–3*). A standard procedure was developed and has been tested on a wide range of material over a 2-year period. It has given reasonably consistent estimates of the dormancy or germinability of nearly all lots of gladiolus cormels tested. In some instances, where germination tests gave a low proportion of emergence and the tetrazolium tests suggested a higher degree of germinability, the corms were found to have impermeable coats. When the husks were removed or cracked, germination rose to a level concordant with the results of the tetrazolium test.

The standard procedure is as follows. (1) A 1% aqueous solution of 2-3-5 triphenyltetrazolium chloride is prepared and kept in a stoppered bottle in the dark at room temperature. (2) A single sheet of filter paper is placed in each of 2 Petri dishes and soaked with solution. The minimum amount required is about 2½ ml per dish. The prepared dishes are kept in the dark if not used immediately. (3) Duplicate lots of 20 cormels, representative of the stock under test, are peeled (i.e., the dry husk is removed) and cut longitudinally with a razor blade to expose the central vascular region on one or both halves. Recent tests suggest that peeling may be unnecessary if a little extra tetrazolium solution is put in the Petri dish to allow for absorption by the husks. (4) Each pair of half cormels is placed radially on the outside border of the filter paper, cut surface down. Twenty pairs about fill the perimeter of the paper. Two dishes are thus prepared, each from one of the duplicate lots of 20 cormels. (5) The dishes are placed in the dark at approximately 70° F to incubate for 4 hr. (6) The cormels are rated according to the extent and intensity of the red color developing in the vascular region through the center of the cormel, and any additional coloration throughout the storage tissues. The rating given for the whole cormel is that of the half cormel with the more pronounced coloration. The rating standard may be described as follows. A value of zero is given to a cormel when there is no observable pink or red color from the dye; a faint coloration along the central vascular strand is rated 1; medium to strong color of the vascular strand, 2; strong color of the vascular strand plus some coloration throughout part of the parenchymatous storage tissues, 3; intense coloration of the central strand and medium coloration throughout most of the parenchymatous tissues, 4; and intense coloration over the whole surface, 5. The sums of the ratings, which range between 0 and 100 for a single dish, give an estimate of the mean germinability of the lot of corms from which the duplicate samples are taken.

The accuracy obtainable by taking readings with duplicate samples of 20 cormels is all that is required except in very critical work. Apart from samples of abnormally variable cormels significant differences are generally between 6 and 10 units on the 100-unit scale.

When a considerable proportion of the cormels have readings of 3, 4, or 5, satisfactory germination is usually obtained; when most of the cormels are rated 0, 1, or 2, germination is unsatisfactory. The relationship between ratings and germinability varies significantly with variety; some varieties germinate well when the rating is relatively low, others only when the rating is unusually high (Table 1). This difference appears to exist apart from the permeability of the outer coat. However, the degree of variability has not yet been sufficient to cause serious difficulty in predicting germinability. It is possible to discover by trial which varieties are likely to give abnormal readings.

At the time cormels are harvested, the tetrazolium test reveals considerable physiological activity in the

TABLE 1

NUMBER OF CORMELS WITH LOW (0–2) AND HIGH (3–5) TETRAZOLIUM RATINGS COMPARED WITH PERCENTAGE GERMINATION 40 DAYS AFTER PLANTING

Variety	Treatment	Tetrazolium ratings		Percentage germination
		0–2	3–5	
Elizabeth the Queen	Room temperature	39	1	8
	Cold storage	2	38	68
Margaret Beaton	Room temperature	36	4	26
	Cold storage	5	35	77
Leading Lady	Room temperature	40	0	3
	Cold storage	25	15	41
Valeria	Room temperature	40	0	1
	Cold storage	4	36	28

tissues that is not associated with germinability. The color pattern is centered mainly on the parenchymatous tissue and the perimeter of the cormel. As the sheathing husk dries and hardens, the color reaction decreases until the depth of dormancy is reached and hardly any reddening occurs. From that time on, intensity of the reaction to tetrazolium and capacity for germination rise in parallel. The rise may be rapid or slow, depending on the variety and the conditions of storage or treatment.

A description of experiments which led to the application of this method to gladiolus cormels will be published elsewhere by the senior author.

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Mechanism of Suppression of Nontransmissible Pneumonia in Mice Induced by Newcastle Disease Virus[1]

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In 1942 Burnet (*1*) reported that two successive intranasal inoculations of Newcastle disease virus (NDV) produced extensive influenza-like pneumonia in the mouse and that neither the infection nor the lesion could be transferred by serial passage in mice. This unusual host-virus relationship was later studied extensively by Ginsberg (*2*) and by Davenport (*3*), independently. The data obtained by these investigators were in substantial agreement and indicated that the production of pulmonary lesions by a large amount of NDV paralleled many known host-virus interactions that occur in a true viral infection except that demonstrable viral multiplication[2] did not occur (*2, 3*).

In this laboratory (*4*) the microbial product APM was found to exert a definite but transient suppressive effect on the development of pneumonia in mice following infection with influenza A virus. The fact that APM failed to exert any appreciable antiviral effect *in vitro* or *in vivo* prompted studies which led to the demonstration of its capacity to suppress the nontransmissible pneumonia in mice induced by NDV. Extensive studies with pneumonia virus of mice (*5*) and influenza A virus (*6*) as well as with NDV (*2, 3*) have indicated that factors other than viral multiplication per se are involved in the production of lesions. It would appear that in the case of NDV and of influenza A virus, APM might selectively affect such a factor.

The California strain of NDV was used throughout these studies and was propagated in the allantoic sac of embryonated eggs in the usual manner. Infectivity titrations on pooled allantoic fluid were carried out in embryonated eggs as previously described (*7*). The infective titer of mouse lung tissue was determined in a similar manner except that the diluent for homogenized lung tissue contained 500 units each of penicillin and streptomycin/ml to insure bacterial sterility and that all eggs were chilled overnight after 48 hr of incubation before collection of allantoic fluid. Hemagglutination tests were carried out at 4° C (*8, 9*).

Inoculation and injection of mice. Large numbers of albino mice weighing 18–20 g each were inoculated intranasally under light ether anesthesia with 0.1 ml of undiluted allantoic fluid containing 10^9 ID_{50} of NDV. After inoculation of NDV the mice were distributed at random into identical cages, 6–8 mice per cage. The cages were previously marked as control mice or as mice to be injected with APM and with the scheduled date of sacrifice and examination. Injections of APM were made subcutaneously under the loose skin on the backs of the mice. Groups of 10–15 mice each were sacrificed at appropriate daily intervals and the lesion score (*10*) and average weight of the lungs (weight of Petri dish plus 10 lungs less weight of dish after removal of lungs, divided by 10) were recorded (Table 1). The microbial product APM was prepared as originally described (*4*) from culture filtrates of *Achromobacter* sp. 124.

Suppression of pneumonia was readily effected by daily injections of APM. Large numbers of mice were inoculated intranasally with NDV. One half of these received daily subcutaneous injections of 1.0 mg APM

[1] Paper of the Journal Series, New Jersey Agricultural Experiment Station, Rutgers University—The State University of New Jersey, Department of Microbiology. These investigations were supported by a grant-in-aid from the Rutgers Research and Endowment Foundation.

[2] The term viral multiplication as used in this communication is restricted to the formation of new infectious particles. Ginsberg (*2*) has noted that although multiplication of incomplete virus was not detected, the possibility of its presence could not be definitely eliminated.

TABLE 1

FAILURE OF APM TO AFFECT RESOLUTION OF PNEUMONIA IN MICE

Days after inoculation of NDV*	I/T	Control lesion score L/M	%	I/T	APM† lesion score L/M	%
3	19/19	63/95	66			
7	22/24	56/120	47	20/22	52/110	47

I/T = Number infected/total.
L/M = Total lesion score/total maximum lesion score.
% = L ÷ M × 100.
Lesion score: ½ = 5% lung tissue consolidated; 1 = 5–25%; 2 = 26–50%; 3 = 51–75%; 4 = 76–100%; 5 = dead mouse with lungs consolidated.
* 10^3 ID_{50} intranasally.
† 1 mg APM injected subcutaneously daily beginning on the 3rd day after inoculation of NDV.

beginning 1 hr after inoculation of NDV. The remaining mice served as controls. Twelve to 15 mice from each group were sacrificed daily for 6 days and on the 9th day after inoculation. The lesion score, expressed as percentage pneumonia, and average weight of the lungs were determined as described. The results are presented graphically in Fig. 1. As expected (*2, 3*), the maximum of pneumonia was

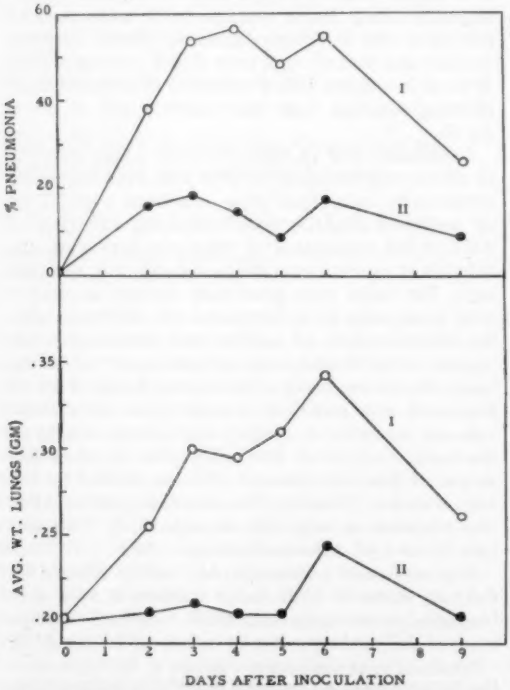

FIG. 1. Effect of daily injections of APM on development of pneumonia. I, control; II, seven daily injections of APM beginning 1 hr after instillation of NDV.

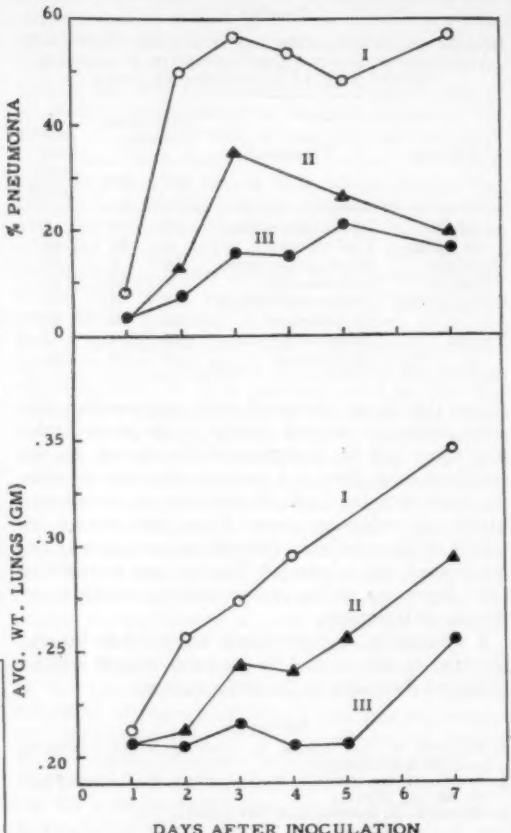

FIG. 2. Effect of early treatment with APM on development of pneumonia. I, control; II, two daily injections of APM beginning 1 hr after instillation of NDV; III, three daily injections of APM.

reached in the control group (curve I) on the 3rd day after inoculation of NDV and severe pneumonia continued for 3 additional days. By the 9th day after inoculation, however, resolution of the pneumonia was well under way. It is evident (curve II) that the pneumonia was considerably reduced in those mice which received 7 daily injections of APM.

When daily injections of APM were discontinued after the second injection, pneumonia continued to develop. In this experiment 17 groups of 12 mice each were inoculated with NDV. Six of these groups were set aside and served as controls. The remaining mice received 2 daily injections of 1.0 mg APM beginning 1 hr after inoculation of NDV. Of these, 5 groups of 12 mice each received one additional injection of APM on the following day (i.e., the 2nd day after inoculation of NDV). Appropriate groups of 12 mice each were sacrificed at daily intervals and the lesion score and average weight of the lungs were recorded. The data (Fig. 2) show that if daily injections of APM were discontinued during the period of rapid

extension of the lesion, pneumonia continued to develop.

When injections of APM were delayed until 48 hr after inoculation of NDV the development of pneumonia was arrested. Large numbers of mice were inoculated with NDV and then separated into 13 groups of 12 mice each. Five these groups were set aside as controls and an equal number received 1.0 mg daily injections for 5 days beginning 1 hr after inoculation. In the 3 remaining groups, daily injections of APM were not begun until 48 hr after instillation of NDV. Appropriate groups of mice were sacrificed daily and the lesion score and average weight of the lungs were noted. The data (Fig. 3) show that daily injections of APM could be delayed for as long as 48 hr after inoculation of NDV and still arrest the development of pneumonia.

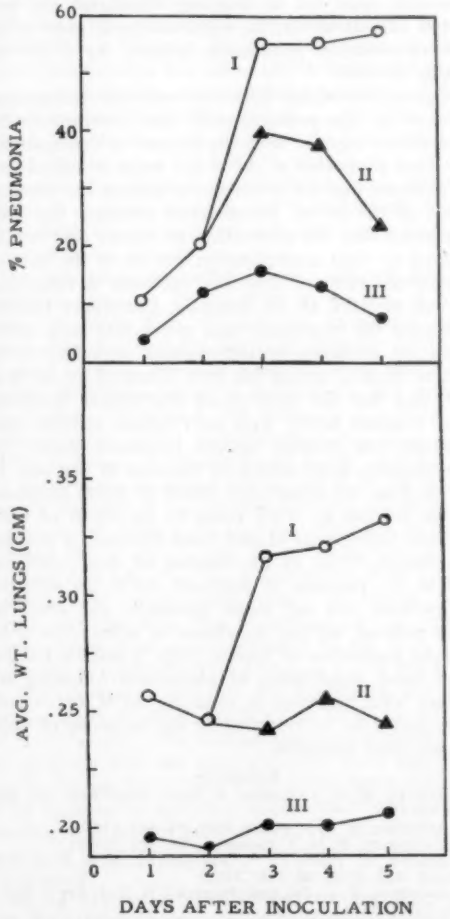

FIG. 3. Effect of delayed administration of APM on development of pneumonia. I, control; II, daily injections of APM begun 48 hr after instillation of NDV; III, daily injections begun 1 hr after instillation of NDV.

However, when daily injections of APM were delayed until the time of maximal pneumonia, i.e., 72 hr after inoculation of NDV, APM was without effect. In this experiment, as before, large numbers of mice were inoculated intranasally with NDV. One group of 19 mice was sacrificed on the 3rd day after inoculation and the lesion score and average weight of the lungs were recorded. A 2nd group of 24 mice received daily injections of 1.0 mg APM beginning on the 3rd day after inoculation. A 3rd group of 22 mice served as controls. On the 7th day after inoculation of NDV mice in the 2nd and 3rd groups were sacrificed and examined (Table 1). It will be seen that APM was without effect when daily injections were delayed for 72 hr and that it did not affect resolution of pneumonia. Thus, it would appear that APM is effective only during the period of rapid extension of the lesion.

Daily injections of APM failed to alter appreciably the infective titer of lung tissue. Eighty mice were inoculated intranasally with 10^9 ID_{50} of NDV. One hour after inoculation 40 mice were injected subcutaneously with 1.0 mg APM and daily thereafter for 2 days. An equal number were set aside as controls. Ten mice from each group were sacrificed 2, 24, 48, and 72 hr, respectively, after inoculation. Lungs from the respective groups were pooled and stored at −70° C. Five to 8 days later the various pools of lung tissue were thawed, 10% suspensions of lung tissue were prepared by grinding lungs from each subgroup in a mortar with sterile sand, and infectivity titrations were carried out in embryonated eggs as previously described (Fig. 4). As expected

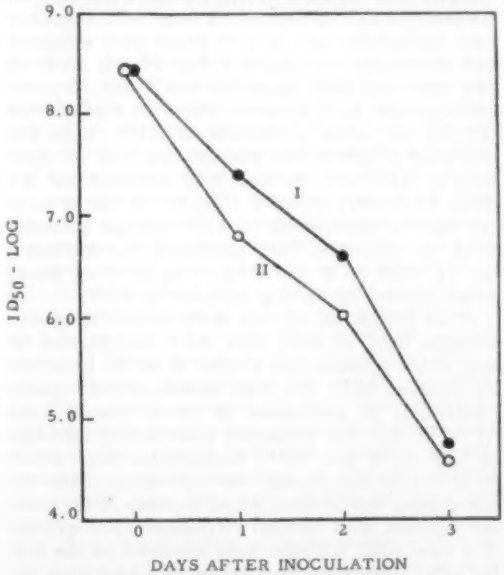

FIG. 4. Effect of daily injections of APM on infective titer of lung tissue. I, daily injections of APM beginning 1 hr after instillation of NDV; II, control.

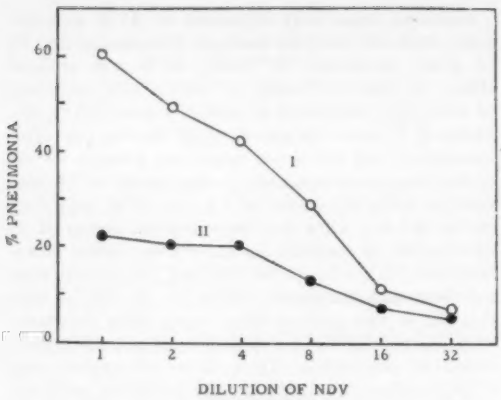

FIG. 5. Effect of dilution of NDV on suppressive action of APM. I, control; II, daily injections of APM beginning 1 hr after instillation of NDV.

(*2, 3*), the infective titer of lung tissue from the control group (curve II) decreased from $10^{-5.4}$ when removed 2 hr after inoculation to $10^{-4.6}$ on the 3rd day after inoculation. Daily injections of APM which definitely suppressed the development of pneumonia failed to affect appreciably the infective titer of lung tissue (curve I).

Curiously, dilution of the inoculum of NDV did not increase the effectiveness of APM in suppressing development of pneumonia. In fact, the data indicate a reduction in effectiveness of APM against limiting dilutions of NDV in the experiment described below. Serial 2-fold dilutions of NDV were inoculated intranasally into 6 groups of 40 mice each. One hour later half of the mice in each group were separated and these mice were injected with 1.0 mg APM at that time and daily thereafter for 2 days. The remaining mice in each group served as controls. On the 3rd day after inoculation of NDV, when the maximum of pneumonia was attained with all dilutions of NDV (*2*), the mice were sacrificed and the lesion scores were recorded (Fig. 5). It will be seen, (a) that the effectiveness of APM was not increased when the amount of NDV inoculated was decreased, and (b) that APM had little or no effect on pneumonia induced by limiting dilutions of NDV.

It will be recalled (*4*) that APM did not inactivate infective NDV *in vitro* when NDV was titrated in eggs in the presence and absence of APM. However, the injurious effect of a large amount of NDV could, conceivably, be neutralized by direct contact with APM. To test this possibility serial 2-fold dilutions of both APM and NDV, respectively, were mixed *in vitro* with one another and with saline. After 90 min at room temperature, 0.1-ml amounts of the various mixtures were instilled intranasally into groups of 5 mice each. All mice were sacrificed on the 3rd day after inoculation and the lesion scores were recorded. Unfortunately, inoculation of concentrations of APM alone of 2.0 mg/ml or higher caused pulmonary consolidation grossly indistinguishable from that caused by NDV. However, maximum tolerated amounts of APM (1.0 mg/ml) failed to inactivate *in vitro* the injurious effect of NDV diluted one-eighth.

The data presented here indicate that the nontransmissible pneumonia in mice induced by the intranasal instillation of a large amount of NDV was definitely modified by subcutaneous injections of APM only during the period of rapid extension of the lesion. However, APM failed to exhibit antiviral (*4*) or antitoxic properties *in vitro*, nor was its effectiveness increased when the inoculum of NDV was decreased. The postulated incomplete virus (*11–14*) has been purposely omitted from consideration in this report in the absence of evidence of its existence in this particular host-virus relationship (*2, 3*). That its presence could not be definitely eliminated has been noted (*2*). However, its relationship, if any, to the nontransmissible pneumonia induced by NDV remains obscure.

Current knowledge (*2, 3*) of host-virus interactions relative to the production of this nontransmissible pneumonia together with the absence of demonstrable antiviral properties of APM (*4*) make it difficult not to conclude that APM selectively inhibits the development of the lesion. Considerable evidence has been presented that the production of lesions may not be related to viral multiplication per se in the case of pneumonia virus of mice (*5*), influenza A virus (*6*), as well as NDV (*2, 3*). Recently, Davenport (*3*) has proposed the hypothesis that cell injury may result from the synthesis or introduction of sufficient infective virus to exceed the level tolerated by the host cell; and that the virus, or its degradation products, may combine firmly with an essential cellular constituent thus creating cellular imbalance leading to hypertrophy, hyperplasia, or necrosis of the cell. If this is true, the suppressive effect of APM on pneumonia induced by NDV could be the result of competition between APM and virus for such a cellular constituent. Thus, in the absence of viral synthesis and in the presence of sufficient APM for effective competition, the cell could gradually rid itself of virus without cellular imbalance or injury and subsequent production of lesions (Figs. 1 and 4). On the other hand, suppression of pneumonia following infection with influenza A virus by APM (*4*) would be expected to be transient in the presence of continuing viral synthesis.

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The Effect of Phenothiazine, N. F. (Green) on the Uptake of I^{131} by the Rat Thyroid[1]

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The drug phenothiazine (thiodiphenylamine) is an anthelmintic in common use by veterinarians in the care of hogs, sheep, and cattle and is frequently used in human treatment. As a regular constituent of the diet of livestock it is often used as a preventive. The use of this drug as an anthelmintic has been reviewed by Davey and Innes (*1*). Collier, in a series of papers, has studied various biochemical effects. The latest of these (*2*) dealt with the inhibitory effect of the drug on succinoxidase and cytochrome oxidase in a beef heart preparation.

Our interest in phenothiazine was aroused by the accidental inclusion of the drug in one lot of our stock rat food; thus without our knowledge, our entire rat colony was fed the drug daily for a period of about 2 weeks. Some of these rats were used in a routine class experiment to demonstrate the uptake of iodine by the thyroid. The failure of the gland to take up iodine (I^{131}) and the concurrent discovery of the inclusion of phenothiazine in the diet led to the following preliminary investigations in the influence of the drug on the uptake of I^{131} by the thyroid.

A group of Sprague-Dawley rats weighing between 150 and 200 g were placed on a Remington iodine-deficient diet (*3*). For the times indicated in Tables 1 and 2, commercial phenothiazine, N. F. (Green) was mixed with the diet. The phenothiazine was added to the salt mixture as recommended by the U. S. Department of Agriculture on a basis of 1 g of the drug to 10 g of salt mixture. In the Remington diet the concentration of drug amounted to 0.1% by weight of the total diet. The average daily consumption of the drug by each rat was calculated to be approximately 100 mg/kg of body weight. This figure appears to be between 50 and 75% higher than that recommended for prophylactic feeding in sheep, but it is only a small fraction of the treatment dose used in livestock.

In the first experiment (Table 1), the drug was added to the food after the animals had been maintained on the Remington diet for 3 days; in the second, more complete experiment (Table 2), the animals were fed the Remington diet for 10 days before the addition of phenothiazine. The I^{131} was administered intraperitoneally 24 hr before the animals were killed. For the animals on phenothiazine for only 24 hr, the I^{131} was administered 2 hr after the drugged food was offered, and, since this was done late in the afternoon, it is assumed that very little food had been eaten by the time the radioactive isotope was administered.

It is obvious from these preliminary experiments that phenothiazine, as it is normally administered to stock animals, has a marked effect on the rat thyroid uptake of I^{131}. Although the data recorded in Table 1 are incomplete, they indicate that the drug produces its effect almost immediately; for, when the drug and the iodine isotope were administered within 2 hr of each other, the thyroids, were found to be suppressed to a degree equivalent to those of animals fed phenothiazine for longer periods of time. This immediate effect was further demonstrated by the lack of significant difference in the uptake of I^{131} by the thyroids of animals fed the drug for 2, 3, or 4 days (Table 2). The difference in the uptake between

TABLE 1

I^{131} Uptake by Rat Thyroid—Remington Diet 6 Days

Groups	No. of animals	Thyroid wt., mg	% Uptake, total gland[1]	% Uptake,[2] mg	Thyroid/blood ratio[3]
Controls	3	17	9.7	0.56	13,500
Phenothiazine 3 days	2	18	0.9	0.05	137
Phenothiazine 2 days	2	19	1.9	0.10	313
Phenothiazine 1 day	2	15	1.3	0.09	860

[1] Radioactivity in total gland ÷ total radioactivity injected.
[2] Radioactivity/mg of thyroid ÷ total radioactivity injected.
[3] Radioactivity/mg of thyroid ÷ radioactivity/ml of blood.

TABLE 2

I^{131} Uptake by Rat Thyroid—Remington Diet 14 Days
(All figures represent the average of 4 animals ± S.E.)

Groups	Thyroid wt., mg	% Uptake, total gland[1]	% Uptake,[2] mg	Thyroid/blood ratio[3]
Controls	16.9 ± 1.6	28.5 ± 5.1	1.85 ± 0.33	26,450 ± 1,291
Phenothiazine 4 days	13.6 ± 1.1	1.6 ± 0.03	0.12 ± 0.04	697 ± 120
Phenothiazine 3 days	14.5 ± 1.6	1.2 ± 0.16	0.09 ± 0.16	598 ± 181
Phenothiazine 2 days	12.4 ± 0.6	1.7 ± 0.15	0.14 ± 0.04	574 ± 212

[1] Radioactivity in total gland ÷ total radioactivity injected.
[2] Radioactivity/mg of thyroid ÷ total radioactivity injected.
[3] Radioactivity/mg of thyroid ÷ radioactivity/ml of blood.

[1] This study was aided in part by a grant from the Atomic Energy Commission.

the experimental and the control animals was highly significant statistically. This degree of suppression of radioiodine uptake was in the same range as that reported by Rawson *et al.* (*4*) when thiouracil was administered as 0.1% of the diet for 16 days to rats maintained on the same diet used here.

Since this drug is widely used as an anthelmintic for livestock and occasionally as such for man, this effect upon the thyroid should be investigated further. It has not as yet been determined whether its action follows that of a typical antithyroid drug, nor is it known what effect the impurities of the commercial preparation have on this action. It also remains to be seen whether other animals, particularly livestock, react as does the rat.

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Albinism Resulting from Certain Carbonic and Thiocarbonic Acid Derivatives of Hydrazine

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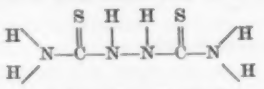
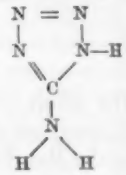
During the course of a research program designed to study the biological activity of various hydrazine derivatives of the carbonic and the thiocarbonic acids and related compounds of high nitrogen content it was discovered that three of these substances, 5-aminotetrazole, bisthiocarbamyl hydrazine, and 1,2-diacetyl-3,5-diamino-1,2,3,5-tetrahydro-1,2,4-thiadiazole induce albinism in plants. This effect is similar to that described by Hamner and Tukey (*1*), and by Ready *et al.* (*2*) who found that albinism is induced by treatment with 3-(α-imino-ethyl)-5-methyltetronic acid and 3-nitro-4-hydroxybenzoic acid, respectively.

Three series of experiments were conducted to evaluate this unusual phenomenon further. In the first series of tests the three compounds were applied to 400 g of soil in unglazed pots at rates approximately equivalent to 60, 25, and 10 lb/acre. Seeds of corn and soybeans were planted simultaneously. A randomized block design with four replications was used. The second group of experiments was designed to test the persistence of these substances in the soil. When the plants in the first test were 45 days old, they were removed from the pots and the pots were replanted without any further addition of chemical. In a third series of experiments, plant species consisting of both crops and weeds growing in greenhouse flats were sprayed with concentrations of 4000 ppm, 2000 ppm, and 1000 ppm until runoff was obtained.

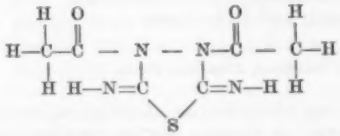
The structural formulas of the three compounds which induced albinism in plants are given as follows:



Bisthiocarbamyl hydrazine



5-Aminotetrazole



1,2-Diacetyl-3,5-diamino-1,2,3,5-tetrahydro-1,2,4-thiadiazole

The blanching effect produced by bisthiocarbamyl hydrazine and 1,2-diacetyl-3,5-diamino-1,2,3,5-tetrahydro-1,2,4-thiadiazole started at the base of the lower leaves and advanced toward the tips. The chlorophyll was gradually removed from the leaves resulting in the death of the entire plant. 1,2-Diacetyl-3,5-diamino-1,2,3,5-tetrahydro-1,2,4-thiadiazole was slower in producing the effect than bisthiocarbamyl hydrazine. Approximately 14 days after treatment with concentrations of 1000 ppm and 4000 ppm of bisthiocarbamyl hydrazine, the corn plants started turning white at the base of the leaves. Plants growing in soil treated with a concentration of 4000 ppm of 1,2-diacetyl-3,5-diamino-1,2,3,5-tetrahydro-1,2,4-thiadiazole started to show a blanching effect approximately 20 days after treatment; the 1000 ppm concentration had very little effect. However, a concentration of 1000 ppm of bisthiocarbamyl hydrazine turned the plants completely white and finally killed them.

Application of bisthiocarbamyl hydrazine to fresh chlorophyll extractions in light resulted in the disappearance of the green color. The addition of an excess of copper sulfate restored the green color. Since bisthiocarbamyl hydrazine complexes metallic ions very effectively, it is believed that the restoration of green color may be due to the removal of the hydrazine derivative as a stable copper complex or to the formation of a copper chlorophyll complex or to both.

Bisthiocarbamyl hydrazine also affects plastid development. Electron microscopic examinations are being carried on at present to study further the mode of action.

5-Aminotetrazole also caused blanching but to a much lesser degree than either bisthiocarbamyl hydrazine or 1,2-diacetyl-3,5-diamino-1,2,3,5-tetrahydro-1,2,4-thiadiazole. The effect of 5-aminotetrazole was found to be temporary, whereas that of bisthiocarbamyl hydrazine and 1,2-diacetyl-3,5-diamino-1,2,3,5-

tetrahydro-1,2,4-thiadiazole was found to be permanent.

Albinism was also induced in plants grown from replantings made 45 days after the initial treatment with 4000 ppm concentrations of bisthiocarbamyl hydrazine and 1,2-diacetyl-3,5-diamino-1,2,3,5-tetrahydro-1,2,4-thiadiazole without any further addition of chemical. This fact demonstrates the strong persistence of the active agent in soil.

Spraying plants with solutions of the three compounds was found much less effective than applying the chemicals directly to the soil. The compounds are apparently systemic in their mode of action in that they are taken up from the soil through the root system with subsequent development of albinism.

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Anterior Choroidal Artery Ligation for Involuntary Movements

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A new procedure for the investigative surgical treatment of involuntary movement disorders has been in use for the past 7 months. Certain significant clinical and physiological consequences of the operation appear to be worthy of note at this time. The procedure consists of an attempt to affect involuntary movement disorders and disorders of muscular tonus by ligation of the anterior choroidal artery. The rationale of this procedure lies in the fact that this blood vessel supplies most of the structures which have been attacked surgically in the attempt to relieve intractable involuntary movements (*1–4*). Among the structures irrigated by this vessel are the globus pallidus, ansa lenticularies, red nucleus, retrolenticular portion of the internal capsule, corpus luysii, substantia nigra, optic tract, and cerebral peduncle (*5*).

We should like to point out that the anterior choroidal artery has been ligated 8 times in 6 patients; the ligations were performed bilaterally in 2 of the cases. In our early studies, we have noted striking alleviations of Parkinsonian tremor at rest in the contralateral extremities. The procedure has been invariably followed by disappearance of most of the rigidity and cogwheelism from the contralateral extremities. There has been no instance of contralateral hemiplegia or hemianesthesia which was previously reported to be invariable following occlusion of this vessel (*6*). Tremor at rest has been relieved in the first patient of this series, since the operation was performed 7 months ago. This technique is believed to be of considerable significance for the future investigative surgery of involuntary movement disorders.

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Effect of Maleic Hydrazide on Auxin-Induced Water Uptake by Pea Stem Segments[1]

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One of the most typical responses of plants to subherbicidal dosages of maleic hydrazide is the repression of terminal growth of stems and roots (*1–7*). Since growth in length is the resultant of meristematic activity and cell enlargement, inhibition of either or both processes will lead to a retardation of apical growth. The experiments of Greulach and Atchison (*2*) with root tips indicate that maleic hydrazide may, in fact, retard either cell division or enlargement, or both, depending upon the concentration of the chemical applied. In some instances, however, cell enlargement seems to be increased by applications of maleic hydrazide, e.g., Struckmeyer (*6*) observed that stems of treated Croft Easter lilies may be shorter but of larger diameter than the controls. In cross section the cells of treated stems appear larger than those of untreated stems, suggesting a change in shape along with possible changes in cell volume. Similar results have been reported by McIlrath (*4*) for the mesophyll cells of treated cotton leaves. Moore (*8*) has shown that maleic hydrazide sprays often have a dehydrating effect on the plant as a whole. Auxin, on the other hand, tends to promote water uptake, in a manner thought to be largely nonosmotic (*9*).

The present study was to elucidate the effect of maleic hydrazide[2] on auxin-induced water uptake in tissues relatively free of meristematic activity. For this purpose, stem segments of pea were chosen as test material, such having been used successfully by Christiansen and Thimann (*10*) in studies on the effect of various inhibitors on growth and water uptake. The techniques of preparing the seedlings were essentially similar to those described by Went and Thimann (*11*) for the split pea stem test for auxin. Seeds of *Pisum sativum* L., var. Alaska, were ger-

[1] Contribution No. 53–6 from the Department of Botany and Plant Pathology, Michigan State College.

[2] The maleic hydrazide used in this work was supplied as the diethanolamine salt by the Naugatuck Chemical Division, U. S. Rubber Co.

minated in silica sand at a constant temperature of 25° C in high-humidity dark chambers. When the seedlings had attained a height of 12–15 cm, 26-mm long segments were removed from the third internodes of the stems and used in the water absorption tests. Each treatment involved 4 replicates of 14 segments, a total of 56, representing 0.95 g of fresh tissue.

Water uptake was determined by rapidly weighing the stem segments and immersing them for 14 hr in 100 ml of the test solution. After this they were removed from the solution, surface-dried, and reweighed. The water absorbed was expressed as a percentage of the original fresh weight. The data thus obtained were submitted to an analysis of variance.

Preliminary tests indicated the importance of aeration and an adequate supply of auxin (indole-3-acetic acid) for rapid water uptake. Aeration was accomplished by passing air into the solutions through sintered aerators at the rate of 2 l of air/min. Maximum water uptake occurred when the concentration of indoleacetic acid was 10 ppm. However, as Leopold and Klein (*12*) pointed out and our own experiments confirmed, the inhibitory effects of maleic hydrazide vary with auxin concentration. Indoleacetic acid at 2 ppm proved adequate for rapid water uptake and was within the range of concentrations where maleic hydrazide at 500 ppm was definitely inhibitory to water absorption.

Although adequate supplies of respiratory substrates are considered essential for active water absorption in many tissues, no additional nutrients were added, with the exception of fumaric acid to be mentioned later. Since continuous rapid water uptake occurred during the 14-hr test period, it is doubtful that substrate exhaustion was a critical factor in these tests of short duration.

The effects of aeration, auxin, maleic hydrazide, and fumaric acid on water uptake by the pea stem segments are shown in Fig. 1. Maximum water absorption occurred only in the presence of adequate auxin and aeration, suggesting a need for high metabolic activity for this process. This observation is in keeping with similar results obtained on many other materials and previously reported in the literature. Concentrations of maleic hydrazide in excess of 250 ppm were definitely inhibitory to water uptake, in the presence of auxin at 2 ppm.

The marked reduction in maleic hydrazide inhibition brought about by fumaric acid (compare F and G) is of interest, although a completely satisfactory interpretation of the effect is not possible at this time. In view of the observation of Naylor and Davis (*13*) that pH changes in the solution are important in determining the degree of inhibition by maleic hydrazide, the pH of the solution before and after addition of the fumaric acid was determined. The pH of the solutions were as follows: auxin alone, 6.4; auxin and fumaric acid, 6.1; auxin, fumaric acid, and maleic hydrazide, 6.6. The change in pH resulting from addition of the fumaric acid was too small to account

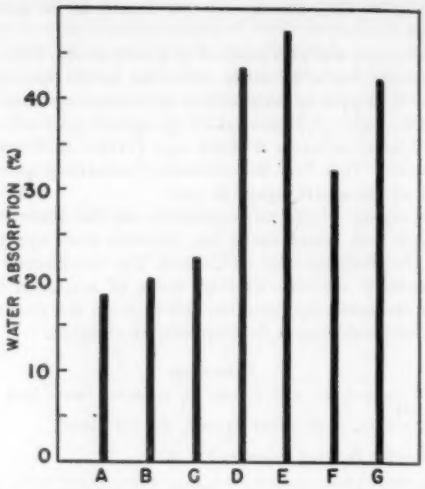

FIG. 1. Water uptake by segments of pea stems in relation to aeration, indoleacetic acid, maleic hydrazide, and fumaric acid. A, distilled water, nonaerated; B, distilled water, aerated; C, 2 ppm indoleacetic acid nonaerated; D, 2 ppm indoleacetic acid, aerated; E, 2 ppm indoleacetic acid, aerated, 0.004 *M* fumaric acid; F, 2 ppm indoleacetic acid, aerated, 500 ppm maleic hydrazide; and G, 2 ppm indoleacetic acid, aerated, 500 ppm maleic hydrazide, 0.004 *M* fumaric acid. Least significant difference between treatments at 0.05 level = 6.1%.

for the observed results. The accelerating effect of fumaric and other organic acids on cell elongation and water uptake is well known (*14, 15*). If, as suggested by Naylor and Davis (*13*), maleic hydrazide operates by inactivating dehydrogenases, several of which participate in the organic acid cycle associated with respiration, it is possible that the formation of fumaric acid and other essential metabolites is blocked by the inhibitor. Addition of such essential materials might circumvent, at least partially, the inhibition of maleic hydrazide.

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Comments and Communications

Gravimetric Thermal Precipitator

I WAS interested to read the account by Kethley, Gordon, and Orr (*1*) of their thermal precipitator for aerobacteriology, since it is similar to one that I have been using in this laboratory for some years as a gravimetric dust sampler for animal inhalation experiments. The design of this instrument is shown in Fig. 1, from which it will be seen that it is of very simple construction. The aluminium hot plate (H) is secured to the aluminium case (N) by the steel sampling tube (A) (steel is used to reduce heat conduction) and nut (B). The heater coil (E) of nichrome tape is covered by an asbestos disc (D), which is secured by the plastic sleeve (C). The ends of the coil are silver soldered to copper wires (F) which are soft soldered to the terminals (G). The aluminium collecting plate (J) is secured by the knurled screw-ring (K) and rubber washer (L), the purpose of which is to take up small dimensional changes resulting from thermal expansion. The gap (O) between the hot and cold plates is about 0.015″ but need not be exact. It is best made by assembling the instrument and then facing the edge of the case and hot plate in one process on a lathe to ensure accurate parallelism.

Details of the performance of the instrument have not previously been published because there are a number of points yet to be worked out, but the following general observations may be of interest.

The performance of a thermal precipitator is governed almost entirely by the power input, and is independent within wide limits of temperature, air gap, or any features of design except those which ensure that as much as possible of the power input is transmitted as heat across the air gap, and that the air flow is uniformly distributed in it. These points can be readily demonstrated by making use of a heater plate with three adjustable projecting screws, and precipitating magnesium oxide smoke on to a glass surface so arranged that it can be watched from outside. It can then be seen that, for a given volumetric flow rate, the diameter of the deposit is fixed by the power input; so long as the deposit is smaller than the hot plate it may be presumed that precipitation is complete. The width of the gap can be varied from 0.005 to 0.0625 in. without appreciably affecting the diameter of the deposit, but if the plate is not parallel to the glass, the deposit will not be circular and dust will escape beyond the edge of the plate at one side. The diameter of the plate affects the diameter of the deposit, but does not affect the power required for complete precipitation at a given flow rate, which for a flow of 100 ml/minute is about 10 watts. It is interesting to compare this with the power required for the thermal precipitator of Green and Watson (*2*) which is about 1 watt for a flow of 6–7 ml/minute, and it would be valuable to have the corresponding

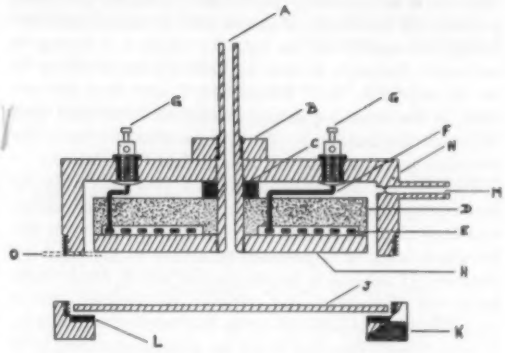

FIG. 1. Gravimetric thermal precipitator.

relationship for the instrument described by Kethley *et al.* and also that previously described by Bredl and Grieve (*3*). I have not attempted to measure the temperature of the hot plate since I found that the performance of the instrument was largely unaffected by whether it was water or air cooled. The temperature of the hot plate is controlled by that of the "cold" surface, and since the effectiveness of thermal precipitation varies inversely as the absolute temperature of the system, water cooling is not worth while unless, as in the case of Kethley *et al.*, it is desirable to keep the temperature of the whole system as low as possible.

I am indebted to C. N. Davies and W. H. Walton for advice on the theoretical aspects of this problem.

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Cosmic Cloud Hypothesis of the Origin of the Solar System

UNDER the above title Palmer (*1*) has recently very severely criticized all present-day theories on the origin of the solar system. As Palmer quotes from one of my papers and from a personal letter from me to him, I felt it worth while to consider the questions which he raises in his letter.

As I see the issues involved, there are two separate

problems. The first one is a factual one: Are the existing theories able to account for all the observed facts? The second one is of a more philosophical nature. Is it scientifically justified to consider in detail a theory of which one is aware that it cannot satisfactorily account for all the data for which it is trying to account? Palmer's answer to both questions seems to be an emphatic "no." Personally, I feel that the answer to the second question should be "yes" and that although the answer to the first question is "no," the situation is not as black as it is pictured by Palmer.

To take the last question first, I feel that only by thoroughly discussing and exploring all possibilities, and thus also the not so very profitable and even the incorrect ones, it is possible to arrive at satisfactory theories. If science is to advance at all, it must needs be by the suggestion and criticism of theories, and it would in my opinion not be in the interest of science, if only "final" theories could be published—even if it were possible to judge prior to publication whether a paper could be considered to give a "final" theory. Palmer's criticism seems therefore to me to be far too severe and to be unscientific.

Regarding the first problem, I fully agree with Palmer that at this moment no completely satisfactory theory exists, and I hope within the near future to give a more detailed account of the reasoning by which I have arrived at this conclusion. However, none of the points raised by Palmer play a role in arriving at this conclusion. His points are mainly concerned with (i) the distribution of angular momentum in the solar system, (ii) the condensation process leading to the planets, (iii) the loss of material from the solar envelope, and (iv) the inclination of the axes of rotation of the outer planets. I do not wish to enter into a detailed discussion at this moment but I may just briefly mention a few points which to my mind are relevant and which seem to have been overlooked by Palmer.

(*a*) The distribution of the angular momentum in the solar system is difficult to understand, but only in as far as the sun is rotating slowly (*2, 3*). It is, however, likely that this problem is not connected with the origin of the solar system, but rather with the more general question of the relation between spectral class and rotation (*4*).

(*b*) If one assumes condensation in the solar envelope to be due completely to supersaturation of part of the constituents (*3, 5*), none of the problems mentioned by Palmer in this connection remains serious.

(*c*) In the discussion of the loss of material from proto-planets or from the solar envelope, Palmer does not seem to take turbulence into account. This would have changed his estimates considerably, as turbulence is probably the most important factor in the development of the solar envelope (*3, 6, 7, 8*).

(*d*) If one takes into account that the height of the solar envelope at the distance from the sun corresponding to Jupiter is at least 10^5 km (*3, 8*), one sees that the problem of the development of the proto-planets is really three dimensional rather than two dimensional and an inclination of the equatorial plane of the outer planets is no longer such an important problem.

Summarizing, it seems to me that even though no completely satisfactory theory has been developed, the situation has certainly been greatly improved by the publication of various theories such as those of von Weizsäcker (*6*), Kuiper (*8*), and Urey (*9*), to name only a few.

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The Somatic Mutation Hypothesis of Cancer Genesis[1]

Copies of Science issued April 24, 1953, contain an article entitled "A Reconsideration of the Somatic Mutation Theory of Cancer in the Light of Some Recent Developments." No original data are presented and quotations only from selected papers appearing in various journals are included, one dated 1951 and the remaining 33 from previous years. The author, Mr. John C. Fardon, says: "In view of the experimental evidence collected in recent years, it may be concluded with some degree of confidence that the somatic mutation theory of cancer does not oppose the facts that have so far been brought to light." With this statement and opinion we most heartily disagree. In support of this contention we wish to call attention first to a later paper by Demerec and coworkers (*1*) which negates the papers by Demerec quoted by Fardon in support of the somatic mutation theory and, second, to personal work (*2–10*) appearing in the literature, reference to which was entirely omitted.

Demerec, Wallace, Witkin, and Bertani (*1*) reported in 1949 that earlier reports on the increased lethal mutation rate in *Drosophila* after administration of carcinogens could not be confirmed. "The variability from experiment to experiment became alarming and only occasionally was it possible to obtain confirmation of previous experiments. The fourth period, encompassing all the past year, has been characterized by uniformly negative results, except in those experiments using nitrogen mustard, methyl-bis

[1] Supported by grants from the National Cancer Institute, U. S. Department of Health, Education, and Welfare.

(β-chloroethyl)amine hydrochloride." It is unfortunate that Demerec's original results are widely quoted and his subsequent retraction is frequently overlooked, possibly due to the restricted circulation of the journal in which it is published.

The effect of 20-methylcholanthrene on lethal mutation rate in the Oregon-R strain of *D. melanogaster* has been tested in our laboratory and reported previously (*2*). No increase in lethals was found after administration of this carcinogen. A scheme (*3*) was then devised for testing mutation rate and tumor incidence simultaneously after treatment of tumor strains of *Drosophila*. Failure to demonstrate an increase in mutation rate in the presence of increased tumor incidence (and vice versa) in this type of experiment should therefore constitute stronger evidence than negative results obtained in the case of either tumor incidence or mutation rate alone. Nitrogen mustard, stilbestrol, methylcholanthrene, and formaldehyde were tested. It was found that mutation rate and tumor incidence were both increased after administration of nitrogen mustard (*4*), only tumor incidence was higher after methylcholanthrene (*5*), only mutation rate was increased in males after formaldehyde (*6*), and neither mutation rate nor tumor incidence were increased after diethylstilbestrol treatment (*7*).

One should require that mutation rate and tumor incidence be correlated to validate the somatic mutation hypothesis. Otherwise one would expect to find four types of agents: those causing increased mutation rate and tumor incidence, those causing only tumor incidence to increase, those causing an increment only in mutation rate, and finally those affecting neither tumor incidence nor mutation rate. The results in *Drosophila* illustrate that these four types of agents do actually exist. In more recent experiments, introduction of the mutator, *hi*, into two tumor strains (*8*) also failed to reveal any correlation between mutation rate and tumor incidence. This eliminates the possibility that results may be explained by failure of the initiating agent to enter the cell. Other work in our laboratory on biochemical mutants in *Neurospora* treated by exposure to 1,2,5,6-dibenzanthracene and 20-methylcholanthrene (*9*) may be more easily explained by selection than any mutagenic effect of the carcinogen.

It is customary to arrive at a conclusion in a scientific problem by reviewing and evaluating all previous work in the light of personal observations. We are not, in this discussion, including a review, since that has been done elsewhere (*10*), but wish to point out omissions in Fardon's paper which we believe weigh heavily against his conclusions. The frailty of reason and limitations of methodology restrain any dogmatic pronouncements on the validity of the hypothesis in question. However, studies to date in our laboratory do not warrant any change in the view we expressed in this journal in 1950: "There would seem to be a reasonable doubt that there is necessarily a connection between mutagenic and carcinogenic effects of an agent or that carcinogens are necessarily mutagens. At the present time there are even more obstacles in accepting without reservation the hypothesis that tumors are the direct result of somatic mutation."

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Regarding the Somatic Mutation Hypothesis of Cancer

IN HIS RECENT article in SCIENCE, "A Reconsideration of the Somatic Mutation Hypothesis of Cancer in the Light of Some Recent Developments," J. C. Fardon[1] makes the following statement, ". . . it may be concluded with some degree of confidence that the somatic mutation theory of cancer does not oppose the facts that have so far been brought to light." This is a cautious, but at the same time a sweeping conclusion which should not go unchallenged.

One of the principal arguments used to support the somatic mutation hypothesis is that cancer tissue when transplanted maintains its character of malignant growth. This is construed to mean that the cancer cell has a new hereditary character (malignancy) and hence has mutated. The same argument might be applied to most differentiated cells in the adult organism, since, when transplanted, differentiated cells usually maintain their essential morphologic and other characteristics. Thus similar reasoning would lead to the conclusion that differentiation also means mutation. But differentiation is an event taking place at just the appropriate time in the developing organism in coordination with other developmental occurrences. Mutation, on the other hand, displays a high degree of randomness and uncertainty; this applies to the somatic mutations that Fardon cites in drawing his parallels with cancer. I do not believe biology can furnish satisfactorily conclusive evidence that differentation is to be explained in terms of mutation (this does not mean, of course, that differentiation is not genetically controlled). Lacking such evidence the transplantability of cancer tissue constitutes only equivocal support for the somatic mutation hypothesis. Remove that support and the analogies drawn

1 SCIENCE, **117**, 441–445 (1953).

between cancer and somatic mutation lose much of their significance.

But leaving aside this uncertainty, strong evidence against the somatic mutation hypothesis is comprised in quantitative studies of the induction of cancers by ultraviolet light. Repeated exposures to ultraviolet light are necessary to induce tumors. If it is assumed that each dose of radiation produces one or more mutant cells each of which proliferates by "unlimited cell division" to form a clone of cancer cells, it may be calculated that (if the proliferation rate is comparable to the growth rate measured after the tumors have appeared) only the first few clones would have any appreciable effect on the growth of the tumor. The rapid proliferation of the initial clones would swamp out any late-appearing clones, and hence after the first few exposures ultraviolet light should have no effect on the time of appearance of the tumor. Yet doses of ultraviolet light continue to accelerate tumor appearance long after the time they should be ineffective if we were dealing with somatic mutations. Furthermore, the data indicate that the process of carcinogenesis is continuous throughout the whole period of tumor development from the first dose of ultraviolet radiation to the appearance of the tumor, and that no sharp separation into periods of induction and growth can be made. These findings are difficult to fit with any form of the somatic mutation hypothesis.[2]

Most of the reasoning regarding the somatic mutation hypothesis disregards the quantitative aspects of tumor growth, and this constitutes an important weakness. Knowledge of the character of the growth rate is essential to the successful extrapolation back in time to the origin of cancer; and in this regard all cancer theories are extrapolations. The lack of such knowledge is a principal hindrance to our understanding the nature of cancer.

Taking these things into account it seems that there is strong evidence against the somatic mutation hypothesis of cancer; that there is a great deal to be learned before we can accept this or any other hypothesis; and that basic studies of growth and differentiation would seem logical (though perhaps far from smooth) avenues of approach to the problem of carcinogenesis.

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Received May 18, 1953.

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IN HIS REVIEW, "A Reconsideration of the Somatic Theory of Cancer" in SCIENCE, (**117**, 441–445 [1953]), John C. Fardon fails to call attention to certain recent publications which indicate that the "manifestations of cellular anarchy," which he ascribes to mutations, may in part be consequent upon the activities of a pathogenic microorganism of pleomorphic nature. The presence of this microorganism has been revealed by special methods described in the two papers listed below, which state that some of its forms are of viral dimensions, and that these forms have been demonstrated within the cytoplasm and the nuclei of cancer cells obtained from human as well as from animal specimens.

(1) "Cultural Properties and Pathogenicity of Certain Microorganisms Obtained from Various Proliferative and Neoplastic Diseases," by Virginia Wuerthele-Caspé, M.D., Eleanor Alexander-Jackson, Ph.D., James Hillier, Ph.D., Roy M. Allen, D.Sc., and Lawrence W. Smith, M.D. *American Journal of the Medical Sciences*, **220**, 638–648 (1950).

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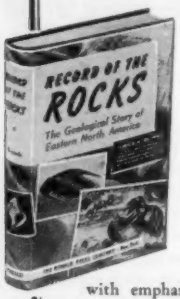

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Aug. 20–30. International Congress of Limnology (12th). Cambridge, England.

Aug. 22–25. Joint Commission on High Altitude Research Stations. Boulder, Colo.

Aug. 23–28. American Dietetic Association. Los Angeles, Calif.

Aug. 24–28. International Congress of Rheumatic Diseases. Geneva, Switzerland.

Aug. 24–29. Oak Ridge Summer Symposium (5th Annual). Oak Ridge, Tenn.

Aug. 24–29. World Conference on Medical Education (1st). London, England.

Aug. 24–31. International Genetics Congress. Bellagio, Italy.

Aug. 24–Sept. 1. World Congress for Sociology. Liége, Belgium.

Aug. 25–27. Gerontological Society (Annual). Mark Hopkins Hotel, San Francisco, Calif.

Aug. 26. Minnesota Academy of Science (Summer). Duluth, Minn.

Aug. 26–28. American Mathematical Society (6th Symposium on Applied Mathematics). Corona, Calif.

Aug. 26–30. American Astronomical Society. Boulder, Colo.

Aug. 28–Sept. 4. International Congress of Tropical Medicine and Malaria. Istanbul, Turkey.

Aug. 30–Sept. 1. American Sociological Society (Annual). University of California, Berkeley.

Aug. 30–Sept. 3. International Society of Orthopedics and Traumatology (6th Congress). Bern, Switzerland.

Aug. 30–Sept. 10. International Congress on the Quaternary, International Association on Quaternary Research. Rome and Pisa, Italy.

Aug. 31–Sept. 2. European Symposium on Cortisone and the Suprarenal Cortex. Milan, Italy.

Aug. 31–Sept. 3. American Hospital Association. San Francisco.

Aug. 31–Sept. 4. Econometric Society. Queen's University, Kingston, Ontario, Canada.

Aug. 31–Sept. 4. International Association for Hydraulic Research. Minneapolis, Minn.

Aug. 31–Sept. 5. World Medical Association (7th General Assembly). Amsterdam, Holland.

Sept. 1–3. Symposium on Plasticity (4th). Brown University, Providence, R. I.

Sept. 1–4. American Institute of Electrical Engineers (Pacific General Meeting). Vancouver, British Columbia.

Sept. 1–5. International Biometric Conference. Bellagio, Italy.

Sept. 1–15. International Congress of Spelaeology. Paris, France.

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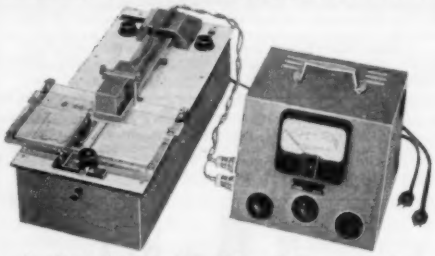

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